URODYNAMICS AND CANINE URINARY INCONTINENCE:
EVALUATION OF A NOVEL ANESTHETIC PROTOCOL
AND TREATMENT STRATEGY

A Thesis
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* * * *

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ABSTRACT

The first objective of this research project was to develop an anesthetic protocol that has minimal effect on urethral pressures measured during urethral pressure profilometry. The second objective was to compare the effect of phenylpropanolamine and pseudoephedrine on the urethral pressure profile of incontinent female dogs using this anesthetic protocol.

Urethral pressure profilometry was performed on 10 normal female dogs in the awake state, under anesthesia with 1.5%, 2.0% and 3.0% end-tidal sevoflurane, and during 0.4, 0.8, and 1.2 mg/kg/min propofol infusion. Measures were taken to maintain a consistent plane of anesthesia for each anesthetized condition. Maximum urethral pressure, maximum urethral closure pressure, functional profile length, and functional area were measured. Results were evaluated using one-way ANOVA and Bonferroni t-test. Mean maximum urethral closure pressure of awake dogs was not significantly different than that of dogs anesthetized with propofol at all infusion rates or sevoflurane at 1.5% and 2.0% end tidal (p ≥ 0.592). Functional area in awake dogs was significantly higher than in anesthetized dogs (p ≤ 0.011). Functional area of dogs during exposure to 3.0% end-tidal sevoflurane was significantly lower than functional area means for other anesthetized conditions (p ≤ 0.028). Individual differences in the magnitude of propofol and sevoflurane effects on urethral pressures were observed. Sevoflurane is an
alternative to propofol for chemical restraint in female dogs undergoing urethral pressure profilometry and produced fewer adverse effects. Use of these anesthetics at appropriate administration rates should reliably distinguish continent from incontinent dogs.

Titration of anesthetic depth is a critical component of urodynamic testing.

Nine female dogs with naturally occurring urethral sphincter mechanism incompetence were treated with either phenylpropanolamine or pseudoephedrine for 28 days with a 14-day washout period between treatments. Order of treatments was randomized in a double-blind cross-over design. Urethral pressure profilometry was performed under 2.0% sevoflurane anesthesia at day 0, 28, 42, and 70. Systolic blood pressure and client-reported continence scores were also assessed at this time. Maximum urethral closure pressure and functional area were significantly increased after treatment with phenylpropanolamine. Maximum urethral closure pressure and functional area were not significantly changed after treatment with pseudoephedrine. Neither medication caused a significant increase in functional profile length or systolic blood pressure. Phenylpropanolamine had a lower occurrence of adverse effects than pseudoephedrine. Phenylpropanolamine caused a significant increase in continence scores but pseudoephedrine did not. Poor correlation was noted between continence scores and urethral pressure profile results in some dogs. Drug metabolism, timing of the urodynamic procedure, and anesthetic-related factors may account for the discrepancy in urethral pressures and owner-reported continence scores in these dogs.

Phenylpropanolamine was found to be more effective than pseudoephedrine in increasing urethral pressures and continence scores in dogs with urethral sphincter mechanism incompetence.
For my family,

without whom the past three years might not have happened,

and for Karl, who despite time and distance continues to be the voice in my head

and the foot at my back.
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Abstract


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CHAPTER 1

LITERATURE REVIEW AND INTRODUCTION

1.1 Literature Review

1.1.1 Neurologic Control of Micturition

Three components of the peripheral nervous system innervate the urethra. The pudendal nerve carries somatic signals to striated muscle that makes up the outer layer of the mid- to distal urethra. The pelvic nerve, which is parasympathetic, and the hypogastric nerve, which is sympathetic, innervate the two smooth muscle layers of the urethra (Figure 1.1). Both the somatic and parasympathetic innervation arise from the sacral spinal cord segments S1-3, whereas the sympathetic innervation arises from the lumbar spinal cord L1-4.\(^1\,^2\)

During the normal filling phase, stretch receptors in the bladder wall send afferent signals along the pelvic nerve, which activate a reflex arc through the hypogastric nerve to the urethra. Norepinephrine (NE) is released by postganglionic neurons to activate \(\beta\)-adrenergic receptors in the bladder wall allowing for relaxation and continued filling. NE also stimulates \(\alpha_1\)-adrenergic receptors in the urethra and causes contraction of the circular and longitudinal smooth muscle of the urethra, thus preventing urine leakage.\(^3\,^4\)

The lateral pontine micturition center in the pons facilitates these adrenergic inputs via descending pathways that target the pre-ganglionic sympathetic neurons in the lumbar
spinal cord that give rise to the hypogastric nerve. Signals from the lateral pontine micturition center also potentiate striated urethral muscle tone. An additional urethral reflex, termed the guarding reflex in humans, is the somatic-mediated contraction of the striated muscle of the urethra in response to a sudden increase in abdominal pressure, such as during a cough or sneeze. Afferent signals travel up the pelvic nerve and initiate efferent signals that travel down the pudendal nerve, releasing acetylcholine (ACh) and activating nicotinic cholinergic receptors that cause contraction of the striated muscle of the urethra.¹

During initiation of micturition, stretch receptors send afferent signals along myelinated fibers of the pelvic nerve. These signals then are transmitted along ascending spinal cord pathways to the medial pontine micturition center. Signals from the cerebral cortex and the hypothalamus are processed to determine if the situation is appropriate for initiation of micturition. The micturition center activates descending spinal cord pathways that subsequently activate parasympathetic neurons in the sacral cord that give rise to the pelvic nerve. Stimulation of the pelvic nerve leads to ACh release from postganglionic parasympathetic neurons in the detrusor muscle of the bladder. ACh binds to M2 or M3 receptors and stimulates bladder smooth muscle contraction. At the same time, inhibitory signals are sent to the sympathetic reflexes and pudendal nerve to allow smooth and striated urethral muscle to relax, facilitating normal emptying.¹,⁵

1.1.2 Urinary Incontinence

Normally, the major component of urethral tone is comprised of smooth muscle. Mucosal integrity, vasculature, and connective tissue surrounding the urethra also play important roles in preserving continence.⁶,⁷ Healthy urothelium is needed to produce a
tight seal within the urethra. Surface tension from glandular secretions and the pliability of the mucosa contribute significantly to coaptation of the urethral walls.\textsuperscript{7} The extensive submucosal vasculature of the urethra also allows for increased pressure to keep the urethra closed. In some studies, up to 30\% of the closure pressure was attributed to thin-walled venous sinuses.\textsuperscript{7,8} Engorgement of these vessels also allows pressure transmission from the surrounding structures to contribute to closure pressure.\textsuperscript{7,8}

Bladder position and the exposure of the urethra to intra-abdominal pressure also are important in preserving continence. When sudden increases in abdominal pressure occur, an increase in pressure occurs both within the bladder and in the proximal and mid-urethra, termed pressure-transmission.\textsuperscript{7,9,10} The pressure increase in the urethra helps to counter the increase in bladder pressure. Several studies have evaluated the position and length of the urethra as well as the vesicourethral angle and the relationship of these parameters to incontinence.\textsuperscript{11-14} It is now commonly accepted that incontinent female dogs tend to have shorter urethras and more caudally placed bladders than continent dogs.\textsuperscript{12,15} There is a large amount of overlap, however, and many continent dogs also have been found to have short urethras and intrapelvic bladders. A study by Atalan and Holt showed a significantly decreased ventral vesicourethral angle in incontinent as compared to continent female dogs.\textsuperscript{14} This finding may indicate a wider bladder neck or abnormal vesicourethral junction, but the implications of this study have not been evaluated. Another study, to evaluate the use of the vagina as a source of intra-abdominal pressure measurements noted that the vaginas of incontinent dogs tended to be more caudally displaced than those of continent dogs.\textsuperscript{16} The caudal displacement also was noted in neutered dogs, and may have been more directly related to neuter status.
rather than incidence of incontinence. Despite lack of definitive evidence for a direct cause and effect relationship, bladder and urethral position appear to be an important risk factor for incontinence.

Several authors have studied the role of neutering in the risk of incontinence. Although the association of neutering with incontinence is no longer debated, the relationship of the timing of the procedure to incontinence is controversial. Arnold and others found that 20.1% of female dogs neutered after the first estrus developed urinary incontinence. In a comparable study, 9.7% of females were found to develop incontinence if neutered before the first estrus. Another group however found the incidence of incontinence to be 3.7% in early neutered females and 9.8% when neutering occurred after the first estrus. Among all investigators there is a general consensus that up to 75% of dogs that develop incontinence will do so within 5 years of neutering.

The relationship of hormone status to incontinence has long been recognized. Post-menopausal women are the highest risk human population for stress incontinence. Estimates have been as high as 43% of women over 50 years of age. Prevalence also appears to increase with number of years post-menopause. In addition to increasing age causing weakening of the pelvic floor and ligamentous support, estrogen deficiency may provide the final "blow" to the continence mechanism. Estrogen receptors are found in the urethral mucosa, vasculature, and in the smooth and striated muscles of the urethra. The supporting ligaments and vaginal wall also have estrogen receptors. Estrogen appears to have a trophic effect on all of these structures. Decreased estrogen concentrations are associated with loss of urethral muscle tone, urethral vascular atrophy, and decreased glandular secretions, affecting major components of the continence
mechanism. Decreased estrogen concentrations may be a factor in the development of incontinence in dogs, but the lack of clinically-recognized incontinence in anestrus intact females points to a more complex mechanism than a simple lack of trophic effect.\textsuperscript{24} Recent evidence suggests the concomitant increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) associated with estrogen decrease also may play a role in the development of incontinence in dogs, but the mechanism has yet to be determined.\textsuperscript{25}

Other risk factors for incontinence are breed, body weight, and tail docking. Among the breeds found to be at increased risk for urinary incontinence are Old English Sheepdogs, Dobermans, German Shepherd Dogs, Boxers, Weimeraners, Rottweilers, and Irish Setters.\textsuperscript{18,20,26} Interestingly, of the breeds evaluated, Labrador Retrievers appeared to have a decreased risk of incontinence, particularly among large breed dogs.\textsuperscript{20} Large and giant breed dogs, and dogs weighing over 20 kg, have been found to have a significantly increased risk of developing incontinence, whereas small breed dogs have decreased risk.\textsuperscript{18,20,26} Tail docking has been suspected to be a contributor to the onset of incontinence because the muscles attached to the tail base, such as the levator ani and coccygeus muscle, often are implicated in the development of the disorder in women. No studies however have directly related tail docking to incontinence.\textsuperscript{20,27} Tail docking is common however, and among the breeds with increased risk of incontinence many females are docked as neonates but develop the disorder only after they are neutered, sometimes as older adults.

Damage to the pelvic floor is considered a major cause of urinary incontinence in women. Multiparous women and those with known injury to the bladder and urethral
suspensory ligaments have a higher rate of incontinence. This finding is substantiated by the success of surgical procedures to repair or replace the support provided by these structures in the treatment of incontinence. Pelvic floor exercises and electrostimulation are considered the first line of treatment for human patients with mild to moderate symptoms. It is controversial whether a similar approach can be applied in dogs with urinary incontinence, because the number of litters or specific damage to the pelvic wall has not shown to be associated with incontinence. The body axis, quadruped vs. biped, represents major difference between dogs and women, but the urethral shortening and abnormal vesicourethral angle which results from loss of pelvic support in women has been seen in incontinent dogs (see above). The relative success of colposuspension in treatment of incontinence in dogs is likely associated with lengthening of the urethra and increased exposure to intra-abdominal pressure transmission, similar to its effects in women.

1.1.3 Urodynamics

In 1961, Enhorning described a method of objectively measuring the urethral closure pressure with respect to the intravesical pressure in the evaluation of urinary incontinence in women. The rationale behind the development of this technique was the theory that in order to maintain continence, urethral pressure must be higher than intravesical pressure during the filling and storage phases of micturition. Urodynamics have evolved since that time in an effort to fully characterize the abnormalities that occur in urinary incontinence. Through the years, much debate has occurred about the methodology of urodynamics, both in the human and veterinary medical fields. Controversy also exists about the utility and role of urodynamics in the diagnosis and
characterization of urinary incontinence. The International Continence Society (ICS) has established standards in the field in order to improve the diagnostic capability of the procedure.28,29

The term ‘urodynamics’ refers to several tests evaluating lower urinary tract function. The three most common tests are the cystometrogram (CMG), the Valsalva leak point pressure (VLPP), and the urethral pressure profile (UPP). The CMG evaluates the integrity of detrusor function and bladder compliance. The bladder is catheterized and slowly filled while measuring intravesical pressure. At a threshold volume, a detrusor reflex occurs and urination will result. The change in pressure as the volume of fluid in the bladder increases indicates the compliance of the bladder. The timing and strength of the detrusor reflex assess its function.

The VLPP is performed in women with the urethral catheter in a static position and pressure measurements taken in both the bladder and the urethra. The patient is asked to slowly “bear down” with a closed glottis in order to increase the intra-abdominal pressure and thus the intravesical pressure. The external urethral meatus is observed and the pressure at which urine leakage occurs is recorded. The VLPP is thought to be a measure of the integrity of the proximal component of the urethral sphincter at the level of the bladder neck.30 This region is most affected in those patients with anatomic stress urinary incontinence. Anatomic stress incontinence refers to the loss of continence associated with poor support of the bladder, urethra, and vagina, whereas functional incontinence refers to abnormalities within the urethral sphincter mechanism itself. Some authors suggest that those patients with primarily anatomic sphincter insufficiency require different treatment strategies than those with functional deficiency, thus making
the VLPP a good predictor of treatment outcome.\textsuperscript{30,31} VLPP has been found to correlate as well or better then UPP parameters with clinical continence scoring. A significant decrease in the VLPP occurs with worsening grade of incontinence in women. The positive predictive value was reported as 73\%, whereas the negative predictive value was 64\%.\textsuperscript{30,32} These low values emphasize the need to evaluate several parameters including a thorough history and physical examination, before making a diagnosis.

Although a traditional VLPP procedure cannot be performed in the dog, a method has been described in which a leak point pressure (LPP) can be determined.\textsuperscript{31} The intra-abdominal pressure is increased by use of a blood pressure cuff and manual pressure, thus slowly increasing the intravesical pressure until leakage is noted. As noted in studies of humans, the volume of fluid in the bladder at the time of the study does not affect the LPP as long as the bladder is not empty or greatly distended.\textsuperscript{31} The LPP has been found to be significantly decreased in incontinent female dogs when compared with continent dogs.\textsuperscript{33}

In human medicine, a commonly used measurement of urethral sphincter integrity is the pressure transmission ratio (PTR). This ratio is the change in urethral pressure divided by the change in intravesical pressure when going from a resting to increased abdominal pressure state. This often is performed during a UPP by having the patient cough or by performing abdominal ballottement in dogs (i.e. a stress UPP). A decreased PTR is seen when the increase in intra-abdominal pressure is not transmitted to the urethra, thus leading to stress incontinence in women. Incontinence in dogs most often is seen at rest, and it would not be expected that the PTR plays a significant role in canine
urinary incontinence. It has been shown, however, that the intravesical pressure in the unsedated dog is higher when recumbent than when standing.\textsuperscript{34}

Several studies have been performed to evaluate the PTR in dogs, but the methodology has not been standardized and results have been divergent. In one study, intra-abdominal pressure was increased by filling the abdominal cavity with N\textsubscript{2}O in order to measure a static PTR.\textsuperscript{35} In this study, no difference in the PTR was found between continent and incontinent dogs. Several other studies, however, that evaluated intermittently increased abdominal pressure in dogs, have shown a better correlation with incontinence.\textsuperscript{13} These studies were performed using the microtransducer method which requires deep anesthesia to avoid artifacts. This anesthetic protocol lowers urethral pressures in both normal and incontinent dogs to $\leq 10$ cm H\textsubscript{2}O, thus preventing a reliable assessment of the relationship between PTR and incontinence.

The UPP measures the pressure within the bladder ($P_{\text{ves}}$), the pressure within the urethra at all points along its length ($P_{\text{ura}}$), and the abdominal pressure ($P_{\text{abd}}$). UPP is performed using a trans-urethral catheter that is withdrawn at a constant rate from the bladder to the external urethral meatus. Pressure is measured in the bladder and urethra by microtransducers mounted on the catheter at various points, or by a perfusion method in which fluid is slowly pumped through the catheter in order to create a fluid “cuff” around the catheter from which to gauge the pressure. A rectal balloon, vaginal, or transabdominal catheter is used to measure $P_{\text{abd}}$. These pressures make up the UPP or curve from which several measurements are taken. The maximal urethral pressure (MUP) is the highest pressure recorded in the urethra as the catheter is withdrawn. The maximal urethral closure pressure (MUCP) is the maximal difference between the
urethral pressure and the intravesical pressure. The functional profile length (FPL) is the length of the urethra over which urethral pressure exceeds bladder pressure. The functional area (FA) is the area under the curve formed by the urethral pressure over the FPL.\textsuperscript{28,35,36} Traditionally, the MUCP and FPL have been the most important of these values and have been found to decrease in patients with incontinence.\textsuperscript{32,37,39} According to ICS standards, the catheter type, withdrawal speed, and perfusion rate (if using the perfusion method) must be reported with the findings.

The clinical use of the UPP in dogs was first described in 1980, but several canine incontinence models had been designed using this procedure before this time.\textsuperscript{40-42} Normal values have been reported for the intact female and intact male dog. The mean MUCP of normal females was found to be 23.9 ± 11.8 mmHg with a range of 13.0 to 46.0 mmHg.\textsuperscript{40} In this study, the dogs were sedated with xylazine to facilitate the placement of the catheters and to minimize artifacts. The perfusion method was used with a flow rate of 2 ml/min and a withdrawal speed of 1 mm/sec. In order to eliminate variability in pressure measurements, the authors evaluated the urethral pressure curve with the catheter in four orientations within the urethra at 90° angles to one another. No predictable variability was noted with respect to the orientation of the catheter within the urethra.

Since the earliest use of UPP in dogs, the effect of anesthetics on the UPP has been a concern. Although several groups, including this author, have reported UPP studies in awake dogs, in most patients it is extremely difficult to adequately perform the procedure in an awake subject without significant artifact.\textsuperscript{31,43,44} Catheterization of
female dogs is difficult without anesthesia, and the sensation of the moving urethral catheter is not well tolerated by many dogs.

Xylazine was the first anesthetic used consistently in the dog for restraint in urodynamic studies. Xylazine was chosen as a sedative because it had been used with success in CMG and was not thought to reduce the contractility of smooth muscle of the bladder. As a $\alpha_2$-adrenergic agonist, it stimulates presynaptic $\alpha_2$-adrenoceptors, which in turn inhibit norepinephrine release from adrenergic nerve terminals such as those in the urethra. This reduces stimulation of the $\alpha_1$-adrenergic receptors that are responsible for a significant portion of urethral tone. Several authors have evaluated the effect of xylazine on the UPP and found significant reductions in the MUCP and FPL when compared to unsedated dogs and those sedated with other drugs.\textsuperscript{43-48} Several alternatives to xylazine have been tried. Opioids were found to reduce urethral pressures as much as xylazine, and had an unpredictable effect on the CMG.\textsuperscript{45} The addition of atropine predictably eliminated the bradycardia associated with xylazine, but did not significantly change the UPP values.\textsuperscript{46} Although specific comparison studies have not been performed, several authors have used a combination of acepromazine, thiopental, and halothane for restraint during urodynamic studies. The values of MUCP and FPL in the continent female dogs from these studies were as much as 90% below those found in unsedated dogs.\textsuperscript{13,35,49,50} The more selective $\alpha_2$-agonist, medetomidine, was evaluated and had similar effects as xylazine on the UPP.\textsuperscript{48}

Until recently, the sedative with the least effect on the UPP while still providing adequate restraint was propofol.\textsuperscript{47} Normal continent dogs had a mean MUCP of 51.0 cm H$_2$O when sedated with propofol, as compared to 79.7 cm H$_2$O, the lowest reported mean
MUCP for unsedated dogs. Unfortunately, propofol is a poor choice for clinical use. Variable metabolism of the drug by different dogs may lead to variable plasma concentrations and depth of anesthesia, thus affecting urethral pressure. The majority of dogs with urinary incontinence are over 20 kg, requiring a large amount of the drug to be infused intravenously over the course of the urodynamic studies. This feature can dramatically increase the cost of the procedure, and reduce its availability in clinical practice. In addition, propofol has several undesirable adverse effects such as idiosyncratic muscle hypertonicity, which can increase artifacts in the study. Several newer inhalant anesthetics currently are under evaluation for use in urodynamic studies. Sevoflurane has been found to be comparable to propofol at 0.65 – 1.0 minimum alveolar concentration (MAC) or to 1.5 – 2.0% end tidal concentration, without adverse effects and at reasonable cost. Isoflurane also has been observed to preserve urethral pressures in continent dogs when used at concentrations of ≤ 1 MAC (March, personal communication).

UPP methodology has not been standardized in veterinary medicine. Most published studies utilized the perfusion method, whereby urethral pressure is measured with a fluid column that surrounds the catheter and transmits the pressure of the urethral wall. The alternative to this method is the microtransducer method, first reported in the veterinary literature in 1990 in a study comparing catheter withdrawal speeds. This method has been found to be reproducible among studies performed on different days, but has not been found to be repeatable. A decrease in successive MUCP measurements also has been noted with the perfusion method. Sphincter mechanism fatigue and variable degrees of anesthetic depth are potential contributing factors to non-
reproducibility of repeated measurements. The microtransducer and perfusion methods have not been directly compared using the same dogs, but they were found to have similar correlation with VLPP and continence scores when evaluated in two studies of incontinent women. In women, under awake conditions, the urethral pressure values obtained with the microtransducer method appeared to be slightly higher than those recorded with the perfusion method, possibly due to drag effect on the membrane of the transducer sensor of the urethral wall, but the statistical significance of this effect was not evaluated. In dogs, the high sensitivity of the microtransducer method, and thus high potential for artifact, necessitates deep anesthesia, which lowers urethral pressures. Studies performed in dogs using microtransducer methods have been performed using thiopentone and halothane anesthesia and have shown very low MUCP values when compared to studies performed using less suppressive anesthetic protocols. Although there does not appear to be a great difference between the methods in unanesthetized humans, the need for deeper anesthesia during microtransducer studies in dogs leads to the conclusion that the perfusion method may provide a more physiological assessment of urethral pressures.

The effect of patient position, withdrawal speed, and rate of perfusion in the perfusion method on the results are three aspects of the UPP that have been evaluated in order to improve standardization. Patient position in veterinary medicine does not appear to be of major importance because the majority of studies are carried out in right or left lateral recumbency. The withdrawal speed was evaluated and at slower speeds the MUCP was found to be slightly lower than at higher speeds. The two speeds compared were 1 mm/sec and 3 mm/sec. At speeds higher than these (> 5 mm/sec), the MUCP in
women is reduced. The most commonly used perfusion rate is 2 ml/min based on the finding that rates above this rate can significantly increase the recorded urethral pressure in humans. This low rate is justified because the purpose of the perfusion is only to provide a transmission medium for the urethral wall pressure, and not to actually distend it.

The relationship of UPP parameters with incontinence and treatment outcome has been evaluated. Gregory and Holt compared a stressed UPP with bladder neck position and resting UPP in normal and incontinent dogs. The stressed UPP is similar to a normal UPP but incorporates brief increases in intra-abdominal pressure during the withdrawal phase. The authors found that stressed UPP and bladder position were the best predictors of continence when taken together. However, the mean MUCP values in the continent and incontinent dogs in this study were 10.3 cm H₂O and 6.21 cm H₂O, respectively. Both values are well below the reported mean awake MUCP value for incontinent dogs (36.9 cm H₂O) and so these results must be interpreted with caution. The impact of suppression of the urethral pressures by anesthesia in dogs confounds accurate interpretation of MUCP results. When pressures are lowered, even in normal patients, the overlap in urethral pressures between continent and incontinent patients increases, thus making it more difficult to correctly classify patients. In awake studies performed by Richter and Ling, incontinent dogs had a significantly lower MUCP than continent dogs (36.91 ± 8.20 cm H₂O and 79.72 ± 4.61 cm H₂O, respectively). Studies performed in awake dogs allow for more physiologic pressures to be obtained, yield more reliable results, and are more likely to reveal a consistent relationship with incontinence.
1.1.4 Treatment

Treatment of urinary incontinence has taken several avenues. Pelvic floor muscle training and medical therapy are considered primary therapy in humans, whereas surgical procedures for the condition in women have been described for over one hundred years. Several of these treatments have been adapted for veterinary use, including sympathomimetic drugs, estrogens, periurethral injections, and colposuspension surgery.

1.1.4.1 Physiotherapy

Pelvic floor training is considered the initial treatment in women with mild to moderate signs of urethral sphincter mechanism incompetence. This approach is based on the theory that urethral sphincter incompetence is secondary to the breakdown of several components of pelvic and urethral anatomy. The exercises do not directly affect the urethral sphincter, and in patients who have cures using only the exercises, the MUCP is not increased. Treatment involves traditional Kegel exercises or electrostimulation of the pelvic floor muscles to improve their resting tone. In addition, several intravaginal devices such as weighted vaginal cones have been developed to improve the utility of these exercises. The exercises are found to be effective in up to 70% of women, but they must be properly performed on a regular basis for life. The only application in veterinary medicine of such pelvic floor training is the use of electrostimulation of the pelvic wall musculature, presumably while the dog is anesthetized. No reports of this treatment are found in the veterinary literature.

1.1.4.2 Medical Therapy

Several classes of drugs have been used in the treatment of urinary incontinence in women and dogs. \(\alpha\)-adrenergic agents, estrogens, anticholinergics, \(\beta\)-adrenergic
antagonists, and serotonin reuptake inhibitors are among the drugs used in the past. Most treatments focus on neurologic control of urethral smooth muscle tone, but some have other effects, both desirable and undesirable.

α-adrenergic stimulation is responsible for up to 60% of urethral tone during filling.\(^4\) α-adrenergic agents act by stimulating α\(_1\)-adrenergic receptors on the urethral smooth muscle. In addition, some drugs in this class, such as ephedrine and phenylpropanolamine, enhance release of NE from sympathetic neurons. During the course of experiments investigating the neurologic control of micturition, several drugs were found to increase urethral pressure. Khanna and others performed UPP on normal dogs while infusing several agents.\(^3\) Ephedrine was found to increase both urethral and systolic blood pressure, comparable to NE, but the duration of effect was longer. They noted that infusion of propanolol further increased urethral pressures, even if the animal already was under the influence of an α-agonist. This effect is secondary to the blocking of competitive sites (β receptors) for the adrenergic agent.\(^3\) The authors concluded that ephedrine or other α adrenergic agents would be a potential treatment choice for patients with urinary incontinence.

Phenylpropanolamine (PPA), an α agonist, has been used for treatment of incontinence in dogs and humans for nearly 30 years. In 1985, Richter and Ling reported on treatment of 11 female incontinent dogs with 1.5 mg/kg PPA three times a day for two weeks. The MUCP in these dogs was measured before and after treatment without sedation. Mean MUCP increased significantly from 36.91±8.20 cm H\(_2\)O pre-treatment to 77.73±8.70 cm H\(_2\)O post-treatment. Post-treatment values were in the normal range
(79.72±4.61 cm H₂O) for unsedated dogs.²⁴ Clinically, all dogs but one had complete resolution of incontinence and the unresolved dog showed improvement. No change in direct arterial blood pressure was noted in these dogs associated with PPA treatment. Adverse effects at 1.5 mg/kg three times per day were not noted in any of the dogs.

Additional studies using PPA have resulted in improvement in clinical signs of incontinence with few adverse effects.⁶⁰-⁶³ Only one double-blinded placebo-controlled study has been reported on incontinent dogs.⁶² In that study, 50 dogs were treated with either PPA or placebo. Unfortunately, urodynamic studies were not performed, but at the end of the study, 85.7% of the dogs treated with PPA and 33.3% of the placebo-treated dogs were dry. Although statistically significant, the large placebo effect is of concern. Urodynamic measurement would have provided a more objective assessment of actual drug effect.

PPA, in both direct and sustained release formulation at 5 to 6 mg/kg twice a day was shown to increase UPP parameters in continent female dogs by 250% as compared to dogs receiving placebo. In addition, there was a consistent decrease in heart rate in those patients treated with this high dose of PPA, but blood pressure measurements were not performed.⁶⁴ This study also found that after 3 to 5 days of oral administration of PPA, both with sustained release and immediate-release formulations, the interruption of dosing for two to three days did not alter the effect. It has been reported that a sustained-release formulation of PPA at a dosage of 1 to 2 mg/kg once a day has been effective in patients refractory to PPA treatment.⁶³ This effect may be due to maintenance of therapeutic serum levels of the drug over the dosing interval with the sustained-release formulation, as compared to the immediate release drug.
The pharmacokinetics of immediate-release oral PPA have been evaluated in dogs. The maximum concentration of immediate-release PPA occurs at 0.89 hours after oral dosing in dogs. The elimination $t_{1/2}$ of immediate-release PPA is approximately 5 hours. When using immediate-release formulations of any drug, the dosage interval should be less than one elimination half-life of the drug. Consequently, the dosage interval for immediate-release PPA should be less than 5 hours in order for the drug to accumulate and reach steady state serum concentrations. The shortest reported dosing interval for immediate-release PPA is 8 hours. The unsatisfactory clinical response to PPA therapy may be due to inadequate maintenance of therapeutic serum concentrations between dosing. A more prolonged time to maximum concentration and the continued release of PPA into the bloodstream with sustained-release PPA leads to longer periods of effective serum concentrations as compared to the immediate-release formulation. For this reason sustained-release formulations of PPA may be more efficacious in patients who appear to be refractory to immediate-release PPA.

Although PPA currently is the drug of choice for dogs with urethral sphincter incompetence, it has lost favor in human medicine. It has been shown to increase the MUCP and reduce symptoms in women, especially when combined with estrogen therapy, but the prevalence of adverse effects in humans has curtailed its use. The most commonly reported adverse effects of PPA in people are hypertension, dizziness, sleep disturbances, anxiety, and restlessness. These and similar adverse effects also have been reported in dogs treated with $\alpha$-agonists. PPA is thought to be associated
with fewer adverse effects as compared to ephedrine and norephedrine, and of the studies evaluating PPA in dogs with urinary incontinence, adverse effects were mild and dose responsive.\textsuperscript{24,60-63}

In the last 20 years, case reports of young women with hemorrhagic stroke after PPA use began to surface. The Hemorrhagic Stroke Project grew out of the concern raised by these reports. In 2000, the group published findings from a group of 702 patients and 1376 controls. The most striking finding was that women between 18 and 49 years of age had an increased risk (odds ratio, 16.58) of hemorrhagic stroke when taking PPA-containing appetite suppressants. In addition, women taking PPA-containing products of any type for the first time had an increased risk (odds ratio, 3.13) of stroke. No increased risk was noted in men.\textsuperscript{69} No reports have been published regarding a risk of stroke in dogs receiving PPA, but the drug should be used with caution in dogs with cardiac disease or hypertension, and blood pressure should be monitored. After these findings were published, the FDA requested that manufacturers voluntarily remove PPA-containing products from the market.\textsuperscript{70} Since that time, PPA has been made available for use in dogs with incontinence by recent manufacturing of new veterinary formulations of PPA.

Other \(\alpha\)-agonists have been evaluated to determine their suitability to treat urinary incontinence in dogs. Pseudoephedrine (PD), a stereoisomer of ephedrine, has been compared with diethylstilbestrol (DES) in incontinent dogs.\textsuperscript{71} 82.4\% of (n = 17) dogs taking PD had complete resolution of signs, whereas 64.5\% of 31 dogs taking DES had complete resolution of signs. Unfortunately, this study was retrospective and response was based only on owner impression. Little additional information is available on the
utility of PD in incontinent dogs. Improvement was reported in 27 of 38 women with sphincter incompetence taking PD, but those who improved had mild disease and there were no objective measurements of improvement.\textsuperscript{72} Although it is readily available over-the-counter, PD currently is not commonly used for treatment of incontinent dogs, and as with all \textalpha-agonists, it is not recommended for use in women to treat incontinence.

Estrogen was one of the first drugs used to treat women and dogs with urinary incontinence. The association of onset of incontinence with menopause led to the theory that estrogen deficiency was the primary cause of the disorder. Estrogen receptors have been found in the bladder and urethra as well as in the supporting structures of the urogenital tract. The decline in estrogen with advancing age and the loss of its trophic effects on the urogenital mucosa, vasculature, and connective tissue are well-documented.\textsuperscript{6,22,73,74} Estrogen has been found to increase the sensitivity of \textalpha-adrenoceptors in urethral smooth muscle to \textalpha-agonist activity.\textsuperscript{21} It also increases vascularity of the urogenital tract when given to post-menopausal women. The vascular bed accounts for up to 33\% of urethral closure pressure in women.\textsuperscript{22}

Despite evidence of the effect of estrogen on the urogenital tract, results have been disappointing when it has been used to treat urinary incontinence in women. Numerous reports describe estrogen treatment of urinary incontinence, but few have been blinded and placebo-controlled. Progestagens, which have been shown to decrease urethral pressure, often have been included in the therapy, possibly counteracting any beneficial effect of estrogen on urethral tone. Of the meta analyses that have been conducted in human patients, significant improvements with estrogen therapy have been observed in subjective but not objective parameters.\textsuperscript{22} One study of 24 incontinent and 6
continent women identified increased MUCP and FPL, as well as PTR, in patients treated with estradiol for 3 weeks. Other studies, however, have not supported this finding. Estrogen therapy may however be useful in the treatment of urge incontinence and recurrent urinary tract infection in post-menopausal women, but these effects have not been fully evaluated. At this time, estrogen therapy is not considered in most therapeutic algorithms for urinary incontinence in women.

In dogs, the role of estrogen in the pathogenesis of urinary incontinence is not fully defined. Richter and Ling reported no difference in the concentrations of estrogen in neutered incontinent females and anestrous entire females. However, in a later study, Nickel reported a lower concentration of estradiol-17\(\beta\) in neutered females. Nickel also reported that, as the estradiol-17\(\beta\) concentrations increase during the estrus cycle, so does urethral closure pressure. This finding would appear to be strong evidence that estrogen concentrations in dogs are important in the maintenance of urinary continence. In the incontinent dog, the most commonly used estrogen has been DES. Several adverse effects have been associated with the use of DES such as bone marrow suppression, mammary neoplasia, and attractiveness to males. The prolonged action of the drug may be linked to the prevalence of adverse effects. In addition, in the last five years, it has been difficult to obtain this drug. Premarin\(\textregistered\), a conjugated estrogen preparation, has been recommended as an alternative. (DJ Chew, personal communication)

Estriol, a short-acting, naturally-occurring estrogen, recently has been studied in 129 incontinent female dogs. In this study, 82% of the dogs were found to be improved or continent after 42 days of 0.25 to 3 mg estriol daily. Improvement reported by the attending veterinarians correlated well with that reported by the owners. In addition,
hematologic parameters were evaluated in 114 dogs before beginning the study and at day 42 with no abnormalities noted. Minor adverse effects observed included attractiveness to males and vulvar swelling, and these resolved upon dose reduction. Another trial of a smaller number of dogs treated with estriol found that 13 of 20 dogs became continent with few adverse effects. Clearly, a significant population of incontinent dogs responds to estrogen therapy, and estrogens used in combination with α-adrenergic agents can improve continence when either treatment alone has failed. The effects of estriol and other estrogens on the canine UPP have not been investigated.

Recently, a new theory has been presented with regard to the effect of hormone status on incontinence in the female dog. This group noted that in neutered females, LH and FSH are dramatically increased when compared to concentrations in continent entire females. They hypothesized that lack of negative feedback to the pituitary gland had led to these increases. Thus, reducing the LH and FSH concentrations with a gonadotropin-releasing hormone (GnRH) analog may have an impact on continence. They treated 13 dogs that had become refractory to α-adrenergic medication with the GnRH analog deslorelin and PPA, followed by withdrawal of the PPA. In all dogs, the FSH and LH concentrations decreased. Pre-treatment FSH concentrations were not higher than those of intact female dogs. 7 of the 13 dogs were continent for a mean of 247 days, even after withdrawal of the PPA. In 5 of the remaining dogs, addition of PPA led to significant improvement. No adverse effects were noted. Additional placebo-controlled trials will be necessary to determine the effectiveness of this therapy, along with studies to elucidate its mechanism.
In women, few alternatives to surgery are available other than pelvic floor muscle training. The search for new methods of pharmacologic control recently has centered on the Onuf nucleus in the ventrolateral sacral spinal cord at S1-3. Presynaptic terminals innervating motor neurons in this region have high concentrations of NE and serotonin (5-HT). Additional findings indicate that α₁-adrenergic and 5-HT receptors in the Onuf nucleus may facilitate the storage reflex of the striated muscle of the urethra. This finding led to the development of a centrally-acting, selective serotonin/NE reuptake inhibitor, duloxetine.¹ Duloxetine increases the amount of 5-HT and NE available for activation of the 5-HT₂ and α₁-adrenergic receptors in the sacral spinal cord. Excitation of these receptors serves to enhance glutamate activation of motor neurons to urethral striated muscle. The effect of the increased NE and 5-HT is only apparent when the motor neurons are tonically active during bladder filling. For this reason, the adverse effect of urinary retention and dysuria seen with other incontinence therapies is not seen with duloxetine. A placebo-controlled clinical trial of duloxetine in 553 incontinent women resulted in significant improvement in 64% of women taking the drug at higher dosages. No significant difference was observed in the rate of cure compared with placebo. Adverse effects were mild but occurred significantly more often in the duloxetine group as compared to the placebo group. The most frequently reported adverse effects were nausea, headache, somnolence and dizziness.⁶ Duloxetine is a pharmacologic alternative to pelvic floor muscle training for women with urinary incontinence, but urodynamic studies need to be performed in clinical patients to fully assess its effect. No studies have been performed in the dog using centrally-acting serotonin/NE re-uptake inhibitors for the treatment of urinary incontinence.
1.1.4.3 Surgical Therapy

For those patients with poor response to medical treatment, several surgical options exist. In human medicine, these include periurethral injection of bulking agents, suspension procedures, and sling procedures. In veterinary medicine, injection of bulking agents and colposuspension have been studied and used most extensively.

Injection of bulking agents to narrow the proximal urethral lumen has been reported as far back as 1938, when a description of cod liver oil injection was reported. The material is injected into the submucosa of the proximal urethra through a cystoscope or periurethral approach. The periurethral approach has been found to have a slightly higher risk of early complications post-operatively. Two or three blebs are created in the urethral wall, effectively narrowing the urethra. Several agents have been tried, however, little success has been achieved without severe scarring and sloughing, until recently. Teflon® was the first widely used urethral bulking agent in both humans and dogs. The procedure was reported in one study to improve continence in 57% of 298 women treated with just one set of injections. It use decreased after it was found that the Teflon particles migrated after just a few months from the injection site to other parts of the body including the brain, lungs, and lymph nodes. In addition, the Teflon caused a severe inflammatory reaction at the site of injection and often was extruded leaving ulcers in the urethral mucosa. Its use was reported in 22 dogs that had either failed α-agonist therapy or for which such therapy was unsuitable. 36% of the dogs treated were continent after the first injection whereas an additional 41% were continent after a second injection. The majority of these dogs required the addition of PPA to maintain continence and 14 of the dogs relapsed after 4 to 17 months. Necropsy of three of the
dogs was performed 2 to 11 months after injection and no Teflon was found at sites other than the periurethral tissues. Due to the granulomatous reaction to the material and the development of improved injection materials, Teflon has since been abandoned as a periurethral injection material in women. Teflon is still used, however, as a more economical alternative to cross-linked collagen in large breed dogs by some European clinicians.

Glutaraldehyde cross-linked bovine collagen (GAX) today is the most widely used periurethral bulking agent. Before its use in urology, collagen had been used safely by plastic surgeons and dermatologists, and migration of injected collagen was not observed.\(^{80}\) Rather than causing an inflammatory reaction, the GAX implant is vascularized and invaded by fibroblasts. Fibroblasts lay down new endogenous collagen, stabilizing the implant. No evidence of migration within the body has been found in 10 years of GAX use, and the material is considered safe. The post-operative cure rates have been very good, but as with any injectable treatment, long-term outcome is poor compared to other surgical procedures.\(^{21,80}\) Several studies report cure rates of 60% to 80%, but this success decreases to 40% after two years.\(^{21,81}\) In one meta-analysis of studies performed before February 2003, it was found that there were no subjective or objective benefits in the outcome when compared to surgery, but few studies were available for analysis.\(^{78}\) The biggest advantage of collagen injection is the low morbidity associated with this outpatient procedure. The procedure is especially useful in elderly or frail patients who cannot undergo general anesthesia and surgery.

Only one study has been reported regarding the use of collagen in the incontinent female dog. The study reported 32 spayed females refractory to PPA treatment that were
treated by periurethral collagen injection. 53% of the dogs were continent after one or two injections without the addition of PPA. With PPA, the success rate increased to 75%. No post-operative complications were observed, and six of these dogs were observed to be continent > 30 months after the first injection. At the present time, this procedure is performed at only a few veterinary institutions. Long-term follow-up of a larger cohort of dogs treated with periurethral collagen implants is needed.

The ideal injectable bulking agent should be easily delivered, anatomically stable, safe, biocompatible, non-antigenic, non-carcinogenic, and inexpensive. Several agents on the horizon are nearly ideal in these respects. These include, but are not limited to, carbon-coated zirconium beads, autologous cartilage grafts, silicone microimplants, microballoons, and acellular matrix compounds. (McLoughlin, personal communication) As tissue engineering advances, more potential materials will be tested. The current limitation of injection therapy is the poor long-term outcome, and this obstacle must be overcome by those working to design new injectable agents.

For the majority of women with moderate to severe urinary incontinence, surgery is the most effective option. The hundreds of procedures described can be divided into suspensory procedures and sling procedures. Suspensory procedures generally are used in patients with moderate to severe incontinence, and sling procedures most often are used in patients refractory to previous surgery.

The theory behind suspensory treatment is to re-position the proximal urethra into a more intra-abdominal position, lengthening the urethra and improving pressure transmission. The most commonly performed procedure is the Burch colposuspension. In this procedure, the vaginal fascia is sutured to the prepubic tendon on each side. This
procedure draws the urethra and vagina cranially into the abdomen. The open procedure has been reported to have a 90% success rate, whereas the newer endoscopic technique has a slightly lower success rate.27

Colposuspension has been performed in dogs for the last 20 years. The objective is the same as in humans, specifically movement of the proximal urethra into a more intra-abdominal position. Studies showing an increase in the transmission of intra-abdominal pressure immediately after surgery have reported increased LPP from 120 cm H2O to 169 cm H2O and a decrease in the percentage of negative spikes on stressed UPP.10,83 Resting UPP showed an increase in FPL of 19% and 21%, but whereas one study reported an increase in the MUCP, the other reported a significant decrease.10,83 The change in urethral pressure is interesting in that the procedure does not specifically address this aspect of continence.

Long-term follow-up of dogs after colposuspension surgery identified a post-operative success rate of 53% becoming continent, and only 9% showing no improvement. The remainder showed some improvement. The success rate dropped slightly to 47% after 9 patients relapsed 6 weeks to 15 months after surgery.84 Another follow-up study found that 77% of dogs were dry or greatly improved with medication 1 year after surgery. The study also assessed owner satisfaction with the decision to have surgery. 86% of owners felt pleased with their decision.33

Additional surgical procedures performed in women include tension-free vaginal tape (TVT) and sling procedures. The sling procedures usually involve supporting the bladder in a more anatomically appropriate position. This procedure usually is reserved for those patients with severe injury to their continence support structures or those who
have failed previous surgeries. The TVT procedure follows the same theory of supporting the urethra, but is more available to those with moderate incontinence. A woven mesh is placed under the midurethra to reinforce its ligamentous support from the pubic bone. The advantage of this procedure is that it can be performed with local or spinal anesthesia and requires minimal hospitalization. The vaginal tape procedure has been reported to have a success rate of 65% after 2 years, similar to colposuspension in a randomized trial.

1.2 Introduction

In order to identify sphincter mechanism incompetence, and in order to gauge the effectiveness of medical and surgical therapies for incontinence, an objective measure of continence is needed. The UPP has the potential to fill this role, but many studies have not incorporated the UPP as a measure of functional outcome. Many studies that have used UPP testing have utilized anesthetic protocols that decrease urethral pressures so markedly that results are difficult to interpret. This has clouded the relationship between the MU and continence. Studies evaluating the effect of anesthetic depth on urodynamic measures in animals have not been performed. Furthermore, no studies have examined the effect of variable concentrations of inhalant anesthetics on the UPP. More precise delivery of anesthetic agents and avoidance of excessive anesthetic depth may allow maintenance of more physiological urethral pressures, while improving the ease of performing the procedure. A standardized anesthetic protocol will also facilitate more accurate and objective assessment of treatment effects in patients with urinary incontinence. The primary objectives of the following studies were to develop an
anesthetic protocol that maintains urethral pressures in normal dogs and to utilize this protocol in a comparative study of the effects of PPA and PD on urodynamic and clinical improvement in dogs with USMI.
Figure 1.1: Neurologic control of micturition. (Modified from O'Brien, Neurogenic Disorders of Micturition, Veterinary Clinics of North America: Small Animal Practice - Volume 18, 1988)
CHAPTER 2

COMPARISON OF THE EFFECT OF PROPOFOL AND SEVOFLURANE ON THE URETHRAL PRESSURE PROFILE OF HEALTHY FEMALE DOGS

2.1 Introduction

In clinically normal dogs, urethral pressure exceeds intravesical pressure during all phases of bladder filling and during changes in abdominal pressure. Urinary incontinence occurs when urethral pressure is less than intravesical pressure. Urethral pressure profilometry (UPP) is an effective way to evaluate urethral function and its contribution to urinary incontinence in the female dog. This test measures pressures throughout the urethra from the bladder neck to the external urethral orifice. The maximal urethral closure pressure (MUCP) and functional profile length (FPL) are reliable indicators of urethral competence.86

In humans, UPP is performed in the awake state. Sedation or restraint usually is required in other animals because of frequent movement during testing and artifacts that can affect urethral pressures. Many anesthetic agents markedly decrease urethral pressure, making it difficult to evaluate differences between normal and abnormal dogs. Mean MUCP in healthy unsedated dogs ranges from 79.7 to 110.1 cm H2O.31,43 Xylazine decreased MUCP as much as 52 to 73% as compared with that measured in unsedated
dogs and medetomidine reduces MUCP by 76%. Use of halothane as a primary anesthetic results in MUCP reductions ranging from 45 to 90%, compared with awake dogs.

Propofol has been reported to have the least effect on the UPP in female dogs, lowering closure pressure by approximately 36% (51.0 ± 7.4 cm H₂O) compared with unsedated dogs. Unfortunately, propofol has several adverse effects, including idiosyncratic muscle hypertonicity, that make it less desirable for use as a single anesthetic. Anesthesia with propofol is also difficult to control and can cause inconsistent MUCP measurements.

Newer inhalant anesthetics, such as sevoflurane, have not been evaluated for their suppressive effects on UPP. Sevoflurane may provide a more constant plane of anesthesia, and is less expensive to administer to large breed dogs than propofol. For these reasons, sevoflurane may provide a more reliable and convenient method for restraining patients during UPP, compared with other agents.

The purpose of the study reported here was to compare the effects of sevoflurane and propofol anesthesia on UPP in clinically normal female dogs. Anesthetic drug concentrations were systematically varied for each agent to determine the effect of anesthetic depth on UPP. Recordings in the awake state also were obtained. We hypothesized that sevoflurane and propofol would not significantly decrease urethral pressures, compared with results obtained in the awake state, and that mean MUCP measures for sevoflurane would not be significantly different for those obtained with propofol. We further hypothesized that significant decreases in MUCP would occur as anesthetic depth was increased.
2.2 Materials and Methods

2.2.1 Dogs

10 healthy young adult, sexually intact female Beagles that weighed from 7 to 10 kg were screened for underlying disease and urogenital abnormalities before UPP was performed. Dogs were considered clinically normal on the basis of result of physical examination, neurologic examination, complete blood count, serum biochemical analysis, abdominal radiography, urinalysis, and bacteriologic culture of urine. Dogs were observed for 1 week before the study for perineal soiling and exercise-induced urine leakage.

2.2.2 Urodynamic Procedure

Urethral pressure profilometry was performed by the perfusion method with a triple lumen 9-F urinary catheter. The catheter was placed aseptically in the urethra, and urine was collected for urinalysis and aerobic bacteriologic culture. The catheter was connected to pressure transducers that measured intravesical and urethral pressure. The rectum was evacuated manually and a balloon catheter was placed and advanced to the level of the L6 or L7 vertebra. The balloon was inflated with 3 ml of sterile water, and the rectal catheter was connected to a pressure transducer used to measure intra-abdominal pressure. The urethral catheter was mechanically withdrawn from the urethra at a rate of 1 mm/sec, while the urethra was perfused through the urethral pressure ports with warm (42°C) sterile water at a rate of 2 ml/min with an infusion pump. Bladder volume was adjusted throughout the procedure to maintain intravesical pressure between

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*a Triple lumen catheter, model TLC-9M, Life-Tech Inc, Stafford, TX.
*b Abdominal pressure catheter, model RPC-9PU, Life-Tech Inc, Stafford, TX.
*c Medfusion syringe infusion pump 2010, Medex Inc, Duluth, GA.
2 and 7 cm H₂O. Abdominal, urethral, and bladder pressures were recorded during catheter withdrawal and stored on a computer for subsequent analysis. All measurements and calculations were performed by use of a urodynamic system and associated software.⁴

Maximal urethral pressure (MUP) was recorded during the withdrawal phase of the UPP. The MUCP was calculated as the difference between MUP and perfused intravesical pressure. Traditionally, FPL is calculated as the portion of the UPP tracing during which urethral pressure exceeds intravesical pressure. With the perfusion method, however, initial or baseline urethral pressure is often higher than intravesical pressure, because perfused fluid is delivered through the same catheter port where urethral pressure is measured. Therefore, FPL was measured as the portion of the tracing during which urethral pressure exceeded baseline perfusion pressure. Functional area (FA) was calculated as the area under the FPL curve. Amoxicillin⁵ (22 mg/kg, PO, q 12 hours for 7 days) was administered after each procedure.

2.2.3 Study Design

The UPP studies were performed on all dogs during 7 conditions: awake, anesthetized with sevoflurane⁶ at end tidal (ET) concentrations of 1.5, 2.0, or 3.0%, or anesthetized with propofol⁷ at constant rate infusion (CRI) rates of 0.4, 0.8, or 1.2 mg/kg/min intravenously (IV). While under anesthesia, body temperature (°C), % oxygen saturation of hemoglobin (SPO₂),⁸ ET CO₂ concentration,⁹ and heart and

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respiratory rate were monitored. In addition, jaw tone and palpebral reflex were used to assess the plane of anesthesia. During sevoflurane anesthesia, ET sevoflurane concentration was measured.\textsuperscript{1} A circulating water blanket and infrared heat lamp were used to maintain body temperature between 36.7 and 37.7\textdegree C. Procedures were performed at least 7 days apart in each dog to eliminate interference from previous procedures.

2.2.3.1 Awake State

Dogs were briefly anesthetized with 4 – 6 mg/kg propofol administered IV in order to place the urethral and rectal catheters. The dogs were allowed to recover to the point at which they could maintain sternal recumbency without assistance. All dogs were restrained gently in right lateral recumbency during the UPP procedure.

2.2.3.2 Sevoflurane

An intravenous catheter was placed in the cephalic vein of each dog and anesthesia induced with 4 – 6 mg/kg IV propofol. The dogs were intubated, connected to a semi-closed circle rebreathing system with sevoflurane as the inhalant, and mechanically ventilated.\textsuperscript{1} A capnograph system\textsuperscript{1} connected to the endotracheal tube measured ET inhalant and CO\textsubscript{2} concentration (30 – 35 mm Hg) and respiratory rate. After the urinary and rectal catheters were placed, ET sevoflurane concentration was adjusted to 1.5\%, 2.0\%, or 3.0\%, and a minimum of 10 minutes allowed for gas equilibration before UPP testing. At least 30 minutes elapsed between propofol induction and the start of urethral pressure measurements.

\textsuperscript{1} Capnomac Ultima, Datex Engstrom, Tewksbury, MA.
\textsuperscript{1} Ohio anesthesia ventilator, Ohio Medical Products, Airco Inc, Madison, WI.
2.2.3.3 Propofol

Dogs were anesthetized as described above with 4 – 6 mg/kg propofol administered IV. The dogs were intubated, and ventilated as for sevoflurane. Propofol was administered IV at a rate of 0.4, 0.8, or 1.2 mg/kg/min. UPP measurements were recorded after a minimum of 15 minutes at each infusion rate.

2.2.4 Statistical Analysis

Mean MUP, MUCP, FPL, and FA were calculated for each of the 7 conditions in each dog. Mean values were analyzed using one-way ANOVA to determine if significant differences were present among anesthetic treatments across all dogs. If significant differences were found, a Bonferroni t-test was performed to make pairwise comparisons between treatments. A p-value of < 0.05 was considered significant. All statistical analyses were performed with a statistical software program. Data are reported as mean ± standard deviation.

2.3 Results

All dogs remained clinically normal throughout the study and no dogs were observed to have urinary or fecal incontinence. Serial urine cultures performed at least 3 times on each dog over the study period failed to show clinically relevant (≥ 10,000 cfu/ml) growth of organisms. No abnormalities were observed in the physical parameters monitored during anesthesia, and all dogs recovered normally from the procedures. Two dogs became arousable during catheter replacement after withdrawal at the lowest infusion rate of propofol (0.4 mg/kg/min). An increase in the number of movement artifacts noted on the UPP was observed during the awake studies.

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k SigmaStat, SPSS Inc, Chicago, IL.
2.3.1 Maximum Urethral Pressure

No significant difference was noted between MUP in awake dogs and that of dogs anesthetized with either sevoflurane at 1.5% or 2.0% or propofol at all infusion rates (p ≥ 0.388). Dogs anesthetized with 3.0% sevoflurane had significantly lower MUP than awake dogs (p < 0.001) and those anesthetized with 1.5% and 2.0% sevoflurane (p ≤ 0.047) (Table 2.1). Standard deviations of MUP measurements ranged from 17.5% to 36.4% of the mean and were greatest for measurements taken at 0.8 mg/kg/min and 1.2 mg/kg/min propofol and 3.0% sevoflurane.

2.3.2 Maximum Urethral Closure Pressure

The MUCP of conscious dogs (82 ± 16 cm H₂O) was not significantly different from that of dogs anesthetized with 1.5% or 2.0% sevoflurane or with propofol at all infusion rates (p ≥ 0.872) (Figure 2.1). The MUCP of dogs anesthetized with 3.0% sevoflurane (32 ± 15 cm H₂O) was significantly lower (p < 0.05) than the MUCP of all other anesthetic groups except those dogs anesthetized with 1.2 mg/kg/min propofol (p = 0.065) (Table 2.1). Standard deviations of MUCP measurements ranged from 19.7% to 40.4% of the mean and were greatest for dogs anesthetized with 0.8 and 1.2 mg/kg/min propofol infusions and 3.0% sevoflurane.

The MUCP of individual dogs under propofol at 0.4, 0.8, and 1.2 mg/kg/min is shown in Table 2.1. Although MUCP means at all propofol infusion rates were not significantly different, an anesthetic effect on the MUCP was apparent in some dogs and not others. For example, the MUCP of dog 3 was 89 cm H₂O during the infusion of 0.4 mg/kg/min propofol, 78 cm H₂O during the infusion of 0.8 mg/kg/min propofol, and 58 cm H₂O during the infusion of 1.2 mg/kg/min propofol. The MUCP of dog 6 was 80, 81,
and 78 cm H₂O during the infusions of 0.4 mg/kg/min propofol, 0.8 mg/kg/min propofol, and 1.2 mg/kg/min propofol respectively.

2.3.3 Functional Profile Length

No significant differences were observed among FPL values obtained during any of the anesthetic conditions. However, the mean FPL (7.5 cm) was longer for the dogs in the awake state than during any of the anesthetic conditions and approached significance (p = 0.06) (Table 2.1).

2.3.4 Functional Area

Functional area in conscious dogs was significantly higher than that in anesthetized dogs (p ≤ 0.011) (Table 2.1, Figure 2.2). There was no significant difference in FA among dogs anesthetized with 0.4, 0.8, or 1.2 mg/kg/min propofol, and dogs anesthetized with 1.5% or 2.0% sevoflurane (p ≥ 0.152). Pairwise comparisons between 1.5 and 2.0% sevoflurane identified FA mean differences that approached but did not attain significance (205 ± 56 cm² H₂O, 146 ± 40 cm² H₂O, respectively, p = 0.152). The FA of dogs anesthetized with 3.0% sevoflurane was significantly lower than the FA for any of the other 6 conditions (p ≤ 0.028). The standard deviations of FA ranged from 16% to 36.7% of the means and were greatest for measurements using all infusion rates of propofol.

2.4 Discussion

Assessment of urethral sphincter mechanism incompetence (USMI) is complicated by the effect of anesthetics and sedatives on the UPP, but some form of chemical restraint usually is required in dogs due to excessive movements during the awake state that can interfere with reliable UPP recordings. USMI results when
intravesical pressure exceeds maximal resting urethral pressures. Intravesical pressure, however, is secondarily affected by fluctuations in intrabdominal pressure and by the degree of bladder filling. Increases in bladder pressure while recumbent and decreased urethral striated muscle tone when relaxed are the 2 events that are most highly associated with urine leakage in female dogs with USMI. Consequently, the threshold MUCP at which continence is achieved must be considerably higher than resting intravesical pressure in a laterally recumbent anesthetized patient with a non-distended bladder. Richter and Ling examined MUCP values in awake, incontinent female dogs using methods similar to those in the present study.\textsuperscript{24} Mean awake MUCP was 37 ± 8 cm H\textsubscript{2}O in affected dogs. This value represented a 53.7\% reduction of the mean MUCP obtained in awake, healthy continent female dogs (79.7 cm H\textsubscript{2}O).\textsuperscript{24} An ideal method of chemical restraint for UPP would maintain pressures in normal, continent dogs above the awake incontinence mean of approximately 37 cm H\textsubscript{2}O. Otherwise, considerable overlap might occur in the MUCP of continent and incontinent patients leading to errors in USMI diagnosis.

Sevoflurane at 2.0\% and 1.5\% ET concentration and propofol at all rates of infusion maintained the mean MUCP above 37 cm H\textsubscript{2}O in the present study. Sevoflurane at 3.0\% ET concentration reduced the MUCP below this “continence threshold”. Early studies of UPP in dogs utilized xylazine as the primary method of restraint. Xylazine, however, reduced mean MUCP in continent dogs to 36.8 cm H\textsubscript{2}O\textsuperscript{40} and to 23.0 and 23.3 cm H\textsubscript{2}O in 2 other studies.\textsuperscript{43,47} The large standard deviations in each study (from 20\% to 46\% of the mean) also suggested a variable drug effect among dogs. Later UPP studies using halothane as the maintenance agent after thiopentone induction reported mean
MUCPs in continent dogs that did not exceed 13 cm H$_2$O.\textsuperscript{49,50,86} Propofol produced the least effect on MUCP in normal dogs (51 ± 8.0 cm H$_2$O).\textsuperscript{47} Propofol anesthesia in our study yielded similar MUCPs ranging from 62 cm H$_2$O at 1.2 mg/kg/min CRI to 72 cm H$_2$O at 0.4 mg/kg/min CRI. The awake mean MUCP in the same dogs was 82 cm H$_2$O.

Propofol maintained urethral pressures in the dogs of the present study, but use of propofol anesthesia for UPP recordings has a number of disadvantages. Even though a constant rate infusion of propofol was used, variable plasma concentrations of propofol due to variations in drug metabolism could have impacted urethral pressures. As plasma concentration of propofol cannot realistically or practically be monitored and regulated, planes of propofol anesthesia in different dogs and in individual dogs over time may vary. In a study where propofol was used as the anesthetic agent, 2 of 7 dogs had baseline MUCP values that differed by at least 30% from MUCP values recorded on subsequent catheter withdrawals.\textsuperscript{47} Lack of UPP reproducibility could hinder interpretation of urodynamic function in both continent and incontinent dogs. Propofol also can produce an idiosyncratic syndrome characterized by muscle hypertonicity and tremor that can create movement artifact on UPP recordings.\textsuperscript{51,88} These anesthetic concerns combined with the high cost of propofol, especially in large breed dogs that typically have USMI, make propofol a less than ideal agent for urodynamic testing.

Sevoflurane anesthesia produced a constant plane of anesthesia and permitted reliable UPP measurements to be recorded. At 1.5% and 2.0% ET concentration, mean MUCP values (77 and 63 cm H$_2$O, respectively) were comparable to those obtained with propofol. 3.0% ET concentration reduced the mean MUCP to 33 cm H$_2$O and consequently cannot be recommended for clinical use. 3.0% ET concentration exceeds
the MAC value of sevoflurane (2.4% ET) in dogs and would rarely be necessary in clinical patients. A major advantage of sevoflurane anesthesia is that drug delivery and systemic drug concentration can be precisely regulated. In the present study, maintenance of constant sevoflurane concentrations was achieved by controlling ventilation and by capnographic monitoring of ET concentrations. These procedures can be duplicated in the clinical setting and remove a major confounding variable that hinders comparisons of UPP studies between different laboratories and institutions. Previous studies with other inhalant anesthetics did not describe use of these methods in UPP evaluations. Imprecise control of anesthetic depth during testing could have contributed to the frequently observed low pressures, increased variability, and poor predictive value of the UPP in these studies.

Despite numerous measures taken to reduce experimental factors associated with variability, biological variability was observed in the dogs of this study. Awake MUCP values ranged from 53 cm H₂O (dog 5) to 110 cm H₂O (dog 4) indicating considerable differences in peak pressures generated in individual dogs. A wide distribution of MUCP values for anesthetized dogs also was observed. Dog 5 with the lowest MUCP, however, had a long FPL (9.3 cm) and dog 4 with the highest MUCP had a relatively short FPL (5.6 cm). The combined effect of MUCP and FPL in dog 5 likely contributed to the dog's continence. Dogs 7 and 9 exhibited an anesthetic-related reduction in MUCP for both propofol and sevoflurane that was much more pronounced than that observed in other dogs. In dogs 3, 5, 7, and 9, MUCP decreased in a graded manner as propofol infusion rate increased. In the remaining 6 dogs, a graded effect of propofol concentration was not evident. Individual variability in baseline urethral pressures and
variable sensitivity to anesthetic depth among dogs resulted in MUCP standard deviations that were greater than expected.

Functional area is a calculated measure based on both MUCP and FPL and may be a better measure of urethral sphincter competence for this reason. FA currently is used to more fully characterize USMI in human patients and has been shown to be a useful parameter in assessing urethral function. Both MUCP and FPL contribute to urinary continence and, as observed in several dogs of this study, decreases in MUCP often are offset by increases in FPL and vice-versa. FA values were less variable and more clearly demonstrated the effects of anesthetic depth on urethral function. Awake mean FA was 50% greater than the highest mean anesthetized FA and was significantly greater than all other FA values. Propofol at 0.4, 0.8, and 1.2 mg/kg/min resulted in a gradual sequential reduction of the FA to 66%, 58%, and 53% respectively, of the mean awake FA, but these values were not significantly different. The reduction in FA with increasing depth of sevoflurane anesthesia was more pronounced and consistent. 1.5%, 2.0%, and 3.0% ET sevoflurane concentration resulted in FA reductions of 72%, 51%, and 26% of the mean awake FA. Although only the FA at 3.0% ET was significantly different from other means, differences between FA means at 2.0% and 1.5% ET concentration approached but did not attain significance (p = 0.152). Examination of these anesthetic effects in a larger population of dogs may have yielded significant differences.

Propofol and sevoflurane at clinically relevant rates of administration maintained mean MUCP well above the reported mean for awake incontinent dogs. Functional area measures were more sensitive in detecting an effect of propofol or sevoflurane on UPP and clearly revealed that administration of either anesthetic will reduce urethral
function. An ET sevoflurane concentration of 3.0% in most dogs and CRI of propofol at 0.8 and 1.2 mg/kg/min in some dogs reduced the MUCP to less than the mean reported for awake incontinent dogs.24 Similar findings in a dog with incontinence secondary to other causes would lead to an incorrect diagnosis of USMI. The effect of anesthetic depth on urodynamic measures underscores the necessity of monitoring anesthetic concentrations and of standardizing anesthetic delivery to clinical patients. Unlike propofol, ET sevoflurane concentration can be precisely monitored and regulated. Selection of ET sevoflurane concentrations in the 0.65 to 1.0 minimum alveolar concentration range (1.5% to 2.4%) should not adversely affect urethral pressures in clinically normal dogs. Use of other inhalant anesthetics also may not adversely affect urethral pressures, if anesthetic concentrations are titrated to an appropriate concentration. Reliable and repeatable UPP results will allow meaningful comparisons to be made between continent and incontinent dogs and will increase the predictive value of the UPP.
<table>
<thead>
<tr>
<th></th>
<th>MUP (cm H₂O)</th>
<th>MUCP (cm H₂O)</th>
<th>FPL (cm)</th>
<th>FA (cm² H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>95(17)ᵃ</td>
<td>82(16)ᵇ</td>
<td>7.5(1.80)</td>
<td>283(46)ᵇ</td>
</tr>
<tr>
<td>Propofol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4 mg/kg/min</td>
<td>84(18)ᵃ</td>
<td>72(19)ᵃ</td>
<td>6.00(1.16)</td>
<td>188(59)ᵇ</td>
</tr>
<tr>
<td>0.8 mg/kg/min</td>
<td>82(24)ᵃ</td>
<td>70(24)ᵃ</td>
<td>5.91(1.07)</td>
<td>165(47)ᵇ</td>
</tr>
<tr>
<td>1.2 mg/kg/min</td>
<td>72(24)ᵃᵇ</td>
<td>61(25)ᵃᵇ</td>
<td>6.16(1.07)</td>
<td>148(55)ᵇ</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5%</td>
<td>91(22)ᵇ</td>
<td>77(21)ᵃ</td>
<td>5.98(1.15)</td>
<td>205(56)ᵇ</td>
</tr>
<tr>
<td>2.0%</td>
<td>76(21)ᵃ</td>
<td>63(20)ᵃ</td>
<td>5.88(1.31)</td>
<td>146(40)ᵇ</td>
</tr>
<tr>
<td>3.0%</td>
<td>46(17)b</td>
<td>32(15)b</td>
<td>5.71(1.45)</td>
<td>72(19)c</td>
</tr>
</tbody>
</table>

**Table 2.1:** Urodynamic measurements in normal female dogs in the awake state and at various depths of propofol or sevoflurane anesthesia. All values expressed as Mean (SD). Values with the same superscript lowercase letters are not significantly different from one another (p > 0.05).
Figure 2.1: Mean MUCP (closed circles) and standard deviation (error bars) in awake and anesthetized dogs. Anesthesia groups with the same superscript letter are not significantly different from one another (p > 0.05). A – awake, P1 – 0.4 mg/kg/min propofol infusion, P2 – 0.8 mg/kg/min propofol infusion, P3 – 1.2 mg/kg/min propofol infusion, S1 – 1.5% ET sevoflurane, S2 – 2.0% ET sevoflurane, S3 – 3.0% ET sevoflurane.
Figure 2.2: Mean FA (closed circles) and standard deviation (error bars) in awake and anesthetized dogs. Anesthesia groups with the same superscript letter are not significantly different from one another (p > 0.05). A - awake, P1 - 0.4 mg/kg/min propofol infusion, P2 - 0.8 mg/kg/min propofol infusion, P3 - 1.2 mg/kg/min propofol infusion, S1 - 1.5% ET sevoflurane, S2 - 2.0% ET sevoflurane, S3 - 3.0% ET sevoflurane.
CHAPTER 3

COMPARISON OF THE EFFECT OF PHENYLPROPANOLAMINE AND
PSEUDOEPHEDRINE ON THE URETHRAL PRESSURE PROFILE OF
INCONTINENT FEMALE DOGS

3.1 Introduction

Recent evidence has shown that spontaneous activity of the urethral smooth muscle is responsible for the majority of the closure pressure of the female canine urethra. Therapy for urinary incontinence in female dogs has centered on the use of estrogens and α-agonist drugs in order to increase the tone of urethral smooth muscle. Estrogen compounds increase urethral pressure by increasing the number of α-adrenergic receptors in the urethra, whereas α-adrenergic agonists stimulate the receptors by increasing endogenous norepinephrine release and by direct action on the receptors. In the last 10 years, there has been a trend away from estrogen compounds and towards increased use of phenylpropanolamine (PPA), a non-selective α-agonist that has been proven to increase urethral closure pressure in incontinent dogs.

PPA has been used to treat women and dogs with urethral sphincter mechanism incompetence for the last 30 years. Although it has been effective, recent concerns about adverse effects such as hypertension and an increased risk of hemorrhagic stroke in
women have prompted its withdrawal from the over-the-counter market and stopped its use in women.\textsuperscript{67,69,92} Hemorrhagic stroke in dogs administered PPA has not been reported, and there are no reports of increased risk of hypertension in clinical studies where PPA was used to treat urinary incontinence. The most common adverse effects in dogs are decreased appetite, gastrointestinal upset, and restlessness, the majority of which tend to resolve with dose reduction.\textsuperscript{24,60,62,82} PPA is no longer available over-the-counter, but generic and veterinary preparations are available for use by the veterinary practitioner.

Ephedrine is another $\alpha$-agonist proven to be effective in the treatment of urinary incontinence in female dogs and women, but its use is associated with adverse effects including increased nervousness and excitability.\textsuperscript{3,26,70} Pseudoephedrine (PD), a stereoisomer of ephedrine, has been recommended as an alternative to PPA. Its adverse effects have been reported to be milder than those seen with ephedrine, and there are no reports of hemorrhagic stroke to date.\textsuperscript{71} In addition, PD is available in an over-the-counter preparation as a nasal decongestant.

The urethral pressure profile has been shown to be a reliable measure of the severity of urethral sphincter mechanism incompetence.\textsuperscript{24,38,64,89,91,93,94} It has been used to evaluate the effectiveness of various drugs for treatment of incontinence and to grade severity of disease. No crossover studies have compared the effect of PPA to other treatments in dogs with naturally-occurring urinary incontinence using objective measurements. Furthermore, no reports of the effect of PD on the urethral pressure profile in incontinent female dogs are available. The purpose of this investigation was to compare the effect of PPA and PD on the urethral pressure profile in incontinent dogs in
a double blind crossover study, and to evaluate the occurrence of adverse effects and owner impression of treatment success.

3.2 Materials and Methods

3.2.1 Dogs

Nine spayed female dogs with urinary incontinence and no other evidence of illness were recruited from the patient population at The Ohio State University Veterinary Teaching Hospital and a pool of local referring veterinarians. Complete blood count (CBC), serum biochemical profile, urinalysis, and urine culture also were performed before the first urodynamic study. Any dogs with evidence of urinary tract infection were placed on two weeks of appropriate antibiotic therapy and required to have a negative urine culture before entering the study. Abdominal radiographs were performed to evaluate for any structural abnormalities in the pelvis or lower urinary tract. A cystoscopic examination was performed at the time of the first urodynamic study to evaluate for the presence of ectopic ureters or other anatomic abnormality. In dogs that were receiving estrogen and \( \alpha \)-adrenergic medications before the study, all medications were discontinued at least two weeks before the first urodynamic procedure.

3.2.2 Blood Pressure Evaluation

Each dog had an indirect systolic blood pressure measurement performed before anesthesia for each UPP. Blood pressure was measured using the Doppler method as described."}\(^95\) The mean of three consecutive measurements was calculated.
3.2.3 Anesthesia Protocol

A catheter was placed in the cephalic vein of each dog and anesthesia was induced with 4 to 6 mg/kg IV propofol.\(^a\) The dogs were intubated, connected to a semi-closed circle rebreathing system with sevoflurane\(^b\) as the inhalant, and mechanically ventilated.\(^c\) After the urinary and rectal catheters were placed, sevoflurane concentration was adjusted to 2.0% or 3.0% and a minimum of 15 minutes allowed for gas equilibration before UPP testing. At least 30 minutes elapsed between propofol induction and the start of urethral pressure measurements.

After completion of the urodynamic studies, dogs were given 0.05 mg/kg acepromazine\(^d\) intravenously and cystoscopy was performed as previously described.\(^{96,e}\)

3.2.4 Urodynamic Procedure

Urethral pressure profilometry was performed by the perfusion method using a triple lumen 9F urinary catheter.\(^{97,f}\) The catheter was placed aseptically in the urethra and the dog was placed in right lateral recumbancy. The catheter then was connected to pressure transducers that measured intravesical and urethral pressure. The rectum was evacuated manually and a rectal balloon catheter\(^g\) placed and advanced to the level of the 6\(^{th}\) or 7\(^{th}\) lumbar vertebra. The balloon was inflated with 3 ml sterile water and the rectal catheter was connected to a pressure transducer used to measure intra-abdominal pressure. The urethral catheter was mechanically withdrawn from the urethra at a rate of

\(^a\) Propoflo, Abbot Laboratories, North Chicago, IL
\(^b\) SevoFlo, Abbott Laboratories, North Chicago, IL
\(^c\) Ohio anesthesia ventilator, Ohio medical Products, Airco Inc, Madison, WI
\(^d\) Acepromazine maleate injection, Vedco Inc, St. Joseph, MO
\(^e\) Operating cystoscope, model 27005B, Karl Storz Endoscopy – America, Culver City, CA
\(^f\) Triple lumen catheter, model TLC-9M, Life-Tech Inc, Stafford, TX
\(^g\) Abdominal pressure catheter, model RPC-9PU, Life-Tech Inc, Stafford, TX
1 mm/sec while the urethra was perfused through the urethral pressure ports with 42°C sterile water at a rate of 2 ml/min using an infusion pump. Bladder volume was adjusted throughout the procedure to maintain intravesical pressure between 2 and 7 cm H₂O. Abdominal, urethral, and bladder pressures were recorded during catheter withdrawal and stored on a computer for subsequent analysis. All measurements and calculations were performed using a urodynamic computer system and associated software.

Maximal urethral pressure (MUP) was recorded as the maximal urethral pressure during the withdrawal phase of the UPP. The MUCP was calculated as the difference between MUP and perfused intravesical pressure. Traditionally, FPL is calculated as the portion of the UPP tracing during which urethral pressure exceeds intravesical pressure. When using the perfusion method, however, urethral pressure is always higher than intravesical pressure because perfused fluid is delivered through the same catheter port that measures urethral pressure. Therefore, FPL was measured as the portion of the tracing during which urethral pressure exceeded baseline perfusion pressure. Functional profile area (FA) was calculated as the area under the FPL curve. Amoxicillin (22 mg/kg PO q 12 hours for 7 days) was administered after each procedure.

3.2.5 Treatment

Each dog had UPP performed before treatment with any medication. The dogs then were randomly assigned to receive either 1.5 mg/kg of PD³ or PPA¹ every 8 hours for 28 days. On the last day, another UPP was performed after the dogs received the

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³ Medfusion syringe pump 2010, Medex Inc, Deluth, GA
¹ Urolab Primus IV urodynamic system, Life-Tech Inc, Stafford, TX
¹ Amoxi-tabs, Pfizer Animal Health, Exton, PA
³ Pseudoephedrine, Roxane Laboratories Inc, Columbus, OH
¹ Phenylpropanolamine, Contract Pharmaceutical Corp, Hauppauge, NY
morning dose of medication. Following a wash-out period of 14 days, during which time the dogs received no medication, a third UPP was performed. The dogs then were given the alternate drug at 1.5 mg/kg every 8 hours for 28 days. Again the UPP was performed on the last day after the dogs had received the first morning dose. All dogs had UPP performed within 5 hours of receiving the morning dose of medication. Neither the owners nor the clinicians performing the UPP studies were aware of which drug order any dog was assigned until after completion of the project.

3.2.6 Owner Evaluation

Each owner who participated in the study was required to complete a two-page questionnaire on the day of each UPP procedure (Appendix). The first time the questionnaire was completed, the owners were asked to describe the nature of their dog’s incontinence with respect to frequency, time of day, and length of time since the first episode. In addition, they were asked to comment on any adverse effects noted during the administration of either of the study drugs.

A continence score was assigned to the patients based on these responses according to the following scale.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient is never continent. Dribbles urine when awake as well as when sleeping. Constantly has a wet perineum and leaves urine on surfaces when getting up from a sitting or recumbent position.</td>
</tr>
<tr>
<td>2</td>
<td>Poorly continent. Patient urine soils where it has been sleeping more than 50% of the time. Dribbles urine or has a wet perineum when awake 25 to 75% of the time.</td>
</tr>
</tbody>
</table>
Patient urine soils where it has been sleeping more than 50% of the time. Dribbles urine or has a wet perineum when awake, up to 25% of the time.

Patient urine soils where it has been sleeping up to 50% of the time, but does not dribble urine or have a wet perineum when awake.

Patient is always continent.

3.2.7 Statistical Evaluation

Each of the systolic blood pressure, MUCP, FPL, and FA values from a single UPP study were averaged and the result was considered the value for that parameter at that time point. The mean and standard deviation (SD) for each time point (pre-treatment, washout, post-treatment with PPA, and post-treatment with PD) were calculated. The difference between the value of each parameter and the value for the corresponding baseline was calculated. All values passed a test for normality. A general linear model ANOVA was performed to determine effect of treatment, patient or index time with respect to each dependent variable. When a variable was noted to have significant effect, a one-way ANOVA with Tukey's test of multiple comparisons was performed. A P value of ≤ 0.05 was considered significant. All statistical analysis was performed with a statistical software program.\textsuperscript{m} Values are expressed as mean ± SD.

\textsuperscript{m} Minitab Statistical Software, Minitab Inc, State College, PA
3.3 Results

3.3.1 Dogs

Nine female spayed dogs were admitted to the study. Their mean weight was 33.5 kg (range 20 – 62 kg) and mean age was 4.5 years (range 1 – 9 years). There were three Doberman Pinschers and one each of Collie, Weimeraner, Dalmatian, Brittany Spaniel, Mastiff, and Standard Poodle. The dogs had been incontinent for a mean of 18 months (range, 5 to 48 months). Eight of the dogs had been treated previously with PPA, and two had been treated with diethylstilbestrol. Response to the medication had been complete in one and partial in four. Three dogs, including those treated with diethylstilbestrol, had not responded at all to previous treatment. No abnormalities were noted on CBC or biochemical profile. Eight dogs had a normal urinalysis and negative urine bacteriologic culture. Urinalysis and bacteriologic culture identified an enterococcus infection in one dog that was treated with enrofloxacin\(^a\) for two weeks. A negative culture was obtained before the first urodynamic study in this dog.

Abdominal radiographs disclosed a pelvic bladder in one of the dogs, however, no contrast studies were performed to assess the degree of caudal displacement. Cystoscopic evaluation of the vestibule, urethra, and urinary bladder failed to identify ureteral ectopia in any of the dogs.

One dog was removed from the study after developing increased numbers of ventricular premature complexes while under anesthesia. This abnormality was noted during the washout UPP after the first treatment phase of the study and was not seen during previous anesthetic events. This dog also had the highest pre-treatment systolic

\(^a\) Baytril, Bayer Animal Health, Shawnee Mission, KS
blood pressure (165 mmHg) and was the oldest dog in the group. For purposes of evaluation, only pre- and post-treatment urodynamic, blood pressure, and client observation results associated with one treatment (PD) in this dog were included in statistical analysis.

3.3.2 Urodynamics

Mean pre-treatment MUCP was 17.78 ± 9.48 cm H₂O. Mean FPL was 6.60 ± 1.64 cm, and mean FA was 44.10 ± 22.23 cm² H₂O. Mean washout MUCP was 15.23 ± 9.49 cm H₂O, mean FPL was 6.85 ± 2.68 cm, and mean FA was 36.28 ± 21.53 cm² H₂O. There was no significant difference in any of the parameters between the pre-treatment UPP and the post-washout UPP (Table 3.1).

Mean MUCP after 4 weeks of PPA was 24.88 ± 12.67 cm H₂O (Figure 3.1). Mean FPL was 7.36 ± 3.13 cm, and mean FA was 76.90 ± 42.30 cm² H₂O (Figure 3.2). There was a significant increase in the MUCP (P = 0.034) and FA (P = 0.016) after 4 weeks of PPA therapy. There was no significant change in the FPL after 4 weeks of PPA.

After 4 weeks of PD, mean MUCP was 18.11 ± 12.31 cm H₂O, mean FPL was 6.03 ± 1.47 cm, and mean FA was 46.38 ± 28.88 cm² H₂O (Figures 3.3 and 3.4). There was no significant change in the MUCP, FPL, or FA after 4 weeks of PD therapy.

The mean change in MUCP after PPA therapy was 12.23 ± 11.01 cm H₂O and was significantly higher than the mean change in MUCP after PD therapy, which was – 2.22 ± 10.00 cm H₂O (P = 0.012). The mean change in FA after PPA therapy was 43.76
cm² H₂O and was significantly higher than the mean change in FA after PD therapy, which was −2.04 cm² H₂O (P = 0.008).

3.3.3 Blood Pressure

The mean systolic blood pressure pre-treatment was 128.4 mmHg. There was no significant change in the blood pressure after either the PPA (mean 126.9 ± 16.0 mmHg) or PD (136.9 ± 17.6 mmHg) treatment.

3.3.4 Client Observations

The mean continence score pre-treatment was 2.3. The mean continence score after PPA was 4.1 ± 1.2. The continence score significantly increased after PPA treatment (P = 0.03). The mean continence score after PD was 3.8 ± 1.3 and approached but did not attain significance (P = 0.07). There were three dogs whose owners reported improvement on a medication, while the MUCP and FA were found to have decreased. In one treatment period, a dog was observed to have gotten worse, while the MUCP and FA were found to have increased.

More adverse effects were observed in dogs taking PD than in those taking PPA. Nine adverse events were noted in 5 dogs treated with PD, whereas only two adverse effect events were noted in 2 dogs treated with PPA. The most common adverse effects associated with PD were panting, decreased appetite, and lethargy. Increased shedding and increased appetite each were also seen in one dog. The only adverse effects seen with PPA were hyperactivity and increased panting each seen in one dog.

3.4 Discussion

Previous evaluation of PPA using urodynamic procedures in awake incontinent dogs has been performed.²⁴ In these dogs, the mean pre-treatment MUCP, 36.9 ± 8.20
cm H$_2$O, was higher than mean values we report here. Sevoflurane can reduce urethral pressure in normal dogs and likely contributed to the lower pressures obtained in our study. Another explanation for the reduced pressures may be the severity of incontinence in the dogs of this study. The patients whose owners agreed to participate in this study tended to be those that had not responded favorably to previous therapy and whose owners were looking for another alternative. This self-selected population may be more severely affected than those evaluated by Richter and Ling, and thus have lower MUCP.

PPA was shown to significantly increase continence score, MUCP, and FA in these dogs. PD did not significantly increase the MUCP or the FA, and although the continence scores did increase, the difference was not significant. The MUCP did not increase into the normal range when the dogs were treated with PPA, contrary to a previous study. Post-treatment MUCP values were below those of normal dogs administered a similar concentration of sevoflurane (2.0% end-tidal). Since both the incontinent and normal dogs were under a similar anesthesia protocol, the source of this difference may be due, in part, due to the loss of PPA efficacy in the incontinent dogs. PPA efficacy depends on a number of factors including loss or down-regulation of adrenergic receptors, increased drug metabolism, and timing of UPP measurement. Performance of the UPP too long after PPA dosing may have resulted in the recording of sub-maximal urethral pressures during periods of sub-therapeutic PPA serum concentrations. The time of peak action of PPA after oral administration is $0.89 \pm 0.44$ hours. Based on previously published pharmacokinetic data in dogs, at 5 hours post oral PPA administration, the serum concentration would be only 31% of the peak
concentration. In dogs that had UPP performed at ≥ 5 hours after dosing, urethral pressures would not be expected to coincide with an owner’s perception of improvement. Other factors that may have blunted the MUCP response to PPA are inadequate owner compliance in drug administration and a potentially greater effect of sevoflurane on urethral muscle tone in dogs with USMI compared to normal dogs.

The majority of these dogs previously had been treated with PPA, but only one dog had completely responded to the treatment and three had improved. According to owner observation during the study, three dogs (37.5%) became completely dry, whereas three others (37.5%) were greatly improved when treated with PPA. This response rate is similar to the 65 – 75% response reported elsewhere. PD treatment resulted in three dogs becoming completely dry (33.4%), and three dogs exhibiting improved continence (33.4%). This 66% improvement is only slightly lower than the response to PPA, despite no significant change in the MUCP of these dogs. The reason for this discrepancy is unclear, although pharmacokinetic variables could have impacted UPP measurements and placebo-related effects could have impacted continence scores. Several studies in women and the only placebo-controlled study in dogs have shown a large placebo effect associated with the treatment of urinary incontinence. It is possible that the response seen in both groups had a placebo component. This effect would lead to lower response rates for both treatments as compared to those reported in other studies, possibly due to the severity of disease in these dogs. More placebo-controlled studies are necessary for evaluation of the response to PPA and PD in dogs with severe urinary incontinence.
In contrast to our study in normal dogs using sevoflurane, a capnograph was not used during UPP procedures in dogs with USMI to measure end-tidal sevoflurane concentration. Gas concentration was regulated using the vaporizer gauge setting, calibrated by standard methods. This method measures only the delivery concentration of sevoflurane, as opposed to the steady-state concentrations generated within the patient. This technique may have led to deeper levels of anesthesia than were expected based on the vaporizer setting, thus lowering the urethral pressures. Even small increases in sevoflurane concentration can lead to decreased MUCP and FA.44

The adverse effects reported here were similar to those seen with PPA and ephedra alkaloids in the past.26,60,61 The adverse effects seen, such as decreased appetite and restlessness, were likely secondary to the central effect of enhanced NE release. As in previous reports, hypertension was not observed with PPA use in these dogs.24,98 Although PPA and PD are non-selective adrenergic agonists, none of the adverse effects noted were likely related to the activation of $\alpha_2$ adrenergic receptors.

Traditionally, the MUCP and FPL are the most frequently evaluated parameters of the UPP. It has been shown, however, that the FPL is not significantly affected by changes in anesthetic depth, anesthetic type, or therapy with PPA.24,44 Recently, it has been shown that the FA shows a greater proportional increase than the MUCP with decreasing anesthetic depth.44 In the present study, the MUCP increased by 29% in dogs treated with PPA, whereas the FA increased 43%. The FA incorporates changes in the FPL and the MUCP and may be a better predictor of continence. Correlation of the FA with other parameters such as the leak point pressure should be evaluated to further assess the utility of this measurement in the assessment of urinary continence.
<table>
<thead>
<tr>
<th>Measurements</th>
<th>Normal$^{45}$</th>
<th>Pre-treatment</th>
<th>Washout</th>
<th>PPA</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUCP (cm H$_2$O)</td>
<td>63 ± 20</td>
<td>17.78 ± 9.48</td>
<td>15.23 ± 9.49</td>
<td>24.88 ± 12.67</td>
<td>18.11 ± 12.31</td>
</tr>
<tr>
<td>FPL (cm)</td>
<td>5.88 ± 1.31</td>
<td>6.60 ± 1.64</td>
<td>6.85 ± 2.68</td>
<td>7.36 ± 3.13</td>
<td>6.03 ± 1.47</td>
</tr>
<tr>
<td>FA (cm$^2$ H$_2$O)</td>
<td>146 ± 40</td>
<td>44.10 ± 22.23</td>
<td>36.28 ± 21.53</td>
<td>76.90 ± 42.30</td>
<td>46.38 ± 28.88</td>
</tr>
</tbody>
</table>

Table 3.1: Mean ± SD urodynamic measurements in incontinent female dogs before treatment and after treatment with PPA and PD.
Figure 3.1: MUCP values before and after treatment with PPA.
Figure 3.2: MUCP values before and after treatment with PD.
Figure 3.3: FA values before and after treatment with PPA.
Figure 3.4: FA values before and after treatment with PD.
APPENDIX

BEHAVIOR AND URINATION QUESTIONNAIRE
<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activity level during the day:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td><strong>Activity level at night:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td><strong>Pacing, agitation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td><strong>Panting:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td><strong>Irritability, aggression:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td><strong>Barking/Vocalization:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle tremors, shaking:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td><strong>Lethargy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td><strong>Appetite:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td><strong>Water consumption:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>Same</td>
<td></td>
</tr>
</tbody>
</table>

Please list any other changes noted in your dog:
Urination Behavior Checklist

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Usually</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pet is conscious of its urination (postures to urinate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pet is not aware of urination (dribbles urine while walking, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signals to go outside</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinates indoors in view of owner</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinates indoors when owner is not present</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinates when owner stands over or reaches for the dog</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinates indoors when excited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinates in many different areas of the house</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinates in the same spot in the house (when awake)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinates in sleeping area during sleep (crate, flood, bedding)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinates moderate to large amounts indoors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinates small amounts indoors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Describe the first incident of your pet’s urinary problem:

Describe the most recent incident of your pet’s urinary problem:
BIBLIOGRAPHY


89. Arnold S. Urinary incontinence in castrated bitches. 2. Diagnosis and treatment]. Schweiz Arch Tierheilkd 1997;139:319-324.

90. Van der Werf BA, Creed KE. Mechanical properties and innervation of the smooth muscle layers of the urethra of greyhounds. BJU Int 2002;90:588-595.


