A Minipig Model For Evaluation of The Lower Urinary Tract

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ABSTRACT

An animal model, using mini-pigs has been developed to study the pressure/flow relationships in normal , partially obstructed and de-obstructed animals, while awake and in the normal upright posture. This has been achieved by the use of subcutaneously implanted portacatheters into the bladder and peritoneal cavity to measure bladder(Pves) and abdominal pressure(Pabd) respectively and the use of a sling within a restraining cage to immobilise the animal.

Urodynamic studies were obtained: in 31 animals to establish baseline profiles; in 21 that was partially obstructed at the bladder neck using an artificial sphincter cuff and in 9 animals following removal of obstruction.

Collecting phase: Bladder instability was noted in 11% of normal animals. After one month of obstruction, 80% of animals have developed bladder instability, which reverted to the pre-obstructive state 4 weeks after removal of obstruction.

Voiding phase: The normal baseline voiding parameters were: Popen 19.9±8.1 cm H_2O; Pmax 15.7±6.7 cm H_2O; Piso 51.6±11.0 cm H_2O; Qmax 20.5±6.6 ml/s. There was a progressive increase in detrusor pressures(Popen, Pmax, and Pves) and a decrease in the flow(Q). At 12 weeks of obstruction, Popen increased 4 times; Pmax 6 times; Piso 3 times; and Qmax

decreased 73%. Following removal of obstruction at 12 weeks, Qmax reverted to pre-obstructive level whereas Popen, Pmax, and Piso to varying degrees returned to near pre-obstructive levels at 70%,88% and 93% respectively. Urethral resistance(R, PURR, URA) and bladder strength(WF) increased after obstruction, and returned toward to normal following 12 weeks relief of obstruction.

It is concluded that the mini-pig model allows reliable and reproducible measurement of pressure flow parameters in a conscious state and in the natural posture, and can be used to study the effects of obstruction on the detrusor.

Resumé

Un modèle animal a été développé pour étudier les relations qui existent entre la pression et le debit urinaire chez des "mini-couchons" partiellement obstrués et dé-obstrués. L'étude a été faite lorsque ces animaux normaux etais reveillés et en position debout grâce à l'utilisation d'un "sling" à l'intérieur des cages pour immobiliser et soutenir les animaux. Un "portacath" a été implanté sous-cutané avec des tubes en silastic dans la vessie et la cavité peritoneale pour mesurer la pression vésicale (Pves) et abdominale (Pabd).

Des études urodynamiques ont été obtenues dans 31 animaux pour établir un profile de base. Par la suite, une obstruction partielle chez 21 animaux en utilisant le "cuff" d'un sphincter artificiel placé au col vésical fut crée. Neuf études ont été réalisé chez des animaux après que l'obstruction ait été lévée.

Résultats: Dans la phase de collection, l'instabilité vésicale a été noté dans 11% des animaux normaux. Après un mois d'obstruction, 80% des animaux ont développé l'instabilité vésicale. Ces anomalies se sont normalisées suivant la levée de l'obstruction.

PHASE D'ELIMINATION - Les paramètres de base normaux d'élimination étaient: Popen 19.9 ± 8.1 cm H_2O; Pmax 15.7 ± 6.7 cm H_2O; Piso 51.6 ± 11.0 cm H_2O, Qmax 20.5 ± 6.6 ml/s. Il y eut une augmentation progressive de la pression du détrusor (Popen, Pmax et Pves) et une diminution du debit (Q). A 12 semaines d'obstruction, Popen était augmentée de 4 fois, Pmax de 6 fois, Piso de 3 fois, et Qmax diminué de 73%.

Avec la levée de l'obstruction, après 12 semaines, le Qmax s'est normalisé (niveau pré-obstrué) tandis que Popen, Pmax et Piso se sont approchées du niveau pré-obstrué a 70%, 88%, et 93% respectivement. La résistance uréthrale (R, PURR, URA) et la force vésicale se sont élevées après l'obstruction et se sont normalisées 12 semaines après que l'obstruction a été levée.

En conclusion, le modèle "mini-couchons" permet de reproduire de façon fiable les mesures de pressions debit à l'état conscient et avec une posture naturelle et peut être utilisé pour étudier les effets d'obstruction sur le détrusor.

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INTRODUCTION

Bladder outlet obstruction is one of the most frequent diseases in the lower urinary tract. It occurs in middle aged and elderly men. Urethral obstruction is also encountered in children and women. The obstruction is most often caused by benign prostatic hyperplasia(BPH). BPH is an abnormal growth related to aging, beginning at 40 years of age. The incidence increases from 23 to 88 per cent by the ninth decade(Berry et al,1984). A 40 year-old man has a 10-30% chance of developing prostatic hypertrophy that may require surgical treatment before he reaches the age of 80(Ashley et al,1966; Lytton et al 1968; Glynn et al,1985). Autopsy studies have revealed periurethral adenomas in 100% of patients aged 80 years or more. These figures indicate that glandular hypertrophy may occur without giving rise to either symptoms or signs that require medical attention. Further, surgical treatment of BPH is currently based on symptoms as no single urodynamic parameter has been found to be diagnostic for obstruction, or precise enough to predict the outcome of surgery. Thus a substantial number of men undergo transurethral resection of prostate without definite evidence of obstruction(Andersen, 1982). Among the most common symptoms and findings of BPH are

increased micturition frequency, increased bladder pressure during the micturition contraction, unstable bladder contraction and development of residual urine(Turner-Warwick,et al 1973; Malmgren, et al 1987; Mostwin, et al 1991). Removal of outflow obstruction restores the bladder functions in most patients. However in approximately 25% of the patients, the unstable bladder contractions persist (Malmgren et al,1987), and in 15% no improvement in the symptoms is noted(Turner-Warwick, et al 1973). Sibley(1985) pointed out that the response of the bladder itself to lower urinary tract obstruction plays an important role in the nature of patients symptoms. The outcome of surgery following the relief of the obstruction can be prejudiced by this altered bladder status. However, structural and physiological changes in the bladder in response to obstruction have not been clearly defined. This lack of knowledge has been due to lack of suitable animal models that mimicked the response of the human bladder to obstruction.

In the past, several models of lower urinary tract obstruction have been used to evaluate bladder changes in response to obstruction. Various animals, e.g. guinea pigs, rats, rabbits, mice,pigs and dogs have been utilized(Brendt,1975; Caine,1973; Cass, 1968; Levin,1984;

Mattiasson, 1982; Mostwin, 1991; Rohner, 1978;). Experimental designs have consisted of using either an in-vivo bladder model or an in-vitro whole bladder mount. Outlet obstruction has been produced using silk ligature over a catheter which is subsequently removed(Malkowicz,1986), or metal and plastic rings placed around the urethra to decrease the diameter of the urethra(Mostwin, 1991).

Bladder outflow obstruction has been studied in animal models and in the human with BPH. The main associated findings are hypertrophy of detrusor smooth muscle cells and infiltration of the muscularis by connective tissue such as collagen and elastin(Speakman, 1991). Additional studies have also indicated the significant reduction in autonomic innervation of the detrusor muscle in response to outflow obstruction. This may markedly impair the neuromuscular control of the bladder. It is clear from the previous experimental studies on outlet obstruction that the bladder undergoes rapid and extensive morphological, structural, and contractile changes that would markedly alter the physical characteristics of normal bladder function(Brendt and Stephens,1975; Caine and Superstine,1973; Cass and Hinman,1968; Levin et al 1984; Mattiasson and Uvelius,1982; Rohner et al,1978; Uvelius et al,1984).

The present study was designed using minipigs as our animal model to define urodynamic changes that occur before, during and after removal of obstruction in the conscious state and in the upright posture.

RELATIVE BASIC SCIENCE

A. Anatomy Basis of Micturition

- Muscular apparatus of micturition

Muscular anatomy of the urinary bladder and urethra has been studied in detail, mainly in humans, by gross dissection and by histology(Gil Vernet,1968; Griffiths,1985; Hunter et al 1954; Hutch,1972; Lapides,1958; Uhlenhuth et al 1953; Wesson,1920; Woodburne,1967; Young,1972). Analysis of the observations in these studies, in conjunction with available embryologic, anatomic, neuromorphologic, and physio-pharmacologic observations, led to the proposal (Elbadawi, 1983,1982) that the mammalian muscular apparatus of micturition is composed of four units: the detrusor, the Lissosphincter, and the ureterotrigonal muscle which are composed of smooth muscle; the fourth, the urethral rhabdosphincter is a striated muscle. These units are anatomically interrelated and are functionally integrated throughout the micturition cycle, with specific roles in both the storage and expulsion phases of micturition.

The bladder detrusor was divided into body and base as functional units(Elbadawi and Schenk,1966). The body consists of smooth muscle bundles that continually change their planes of orientation and freely crisscross and interlace with each other without recognizable arrangement as discrete layers. The base consists of trigone and longitudinal detrusor bundles. The smooth muscle of trigone include two distinct layers, termed the superficial and deep trigonal muscle. The predominantly longitudinal muscularis of each distal ureter fans out at the ureteral orifice, extending beyond its floor into the trigonal region. The extensions from both sides blend to from a thin triangular sheet of small and compact muscle bundles, designated as the superficial trigone (Tanagho,1963) or simply as the trigonal muscle (Elbadawi,1982; 1986;1971). The deep trigonal muscle or the trigonal component of the Lissosphincter(Elbadawi,1982) is represented by a triangular muscular structure in the dorsal bladder base detrusor that lies between its outer longitudinal bundles and the trigonal muscle. The longitudinal detrusor bundles spread to all the base units. In the human bladder, interlacing bundles of the detrusor continuing into the bladder base become organized into a ventral and a dorsal group of longitudinal bundles(Gil Vernet,1968; Hunter,1954;Lapides,1958). The ventral group includes two lateral anterior bundles. The dorsal group

include a very prominent posterior and two posterolateral longitudinal components.

It is now known that the wall of the urethra of both sexes in humans and several species incorporates as an integral component, a striated muscle structure that has been designated as the urethral rhabdosphincter(Elbadawi,1974). In the human female, this muscle surrounds the middle third of the urethra as a complete, obliquely circular ring of ± 1.5 cm length that extends cranially to the posterior aspect of the bladder base. The rhabdosphincter of human male consists of caudal, intermediate prostatic, and cranial parts. The caudal part forms a complete ring of obliquely oriented fibres that surround the membranous urethra and intimately related to its smooth muscularis but are separate from the outlying striated musculature of the pelvic floor. Cranial extensions of these fibres form the intermediate prostatic part with variable degrees of obliquity, mainly on the ventral surface of the prostate. Extending cranially from the ventral surface of the prostate, the cranial part of the rhabdosphincter courses on each side of the bladder neck and behind the seminal vesicles to interdigitate with the posterior external longitudinal bundle of the bladder base detrusor.

- Anatomy of extrinsic innervation

The hypogastric and pelvic nerves supply the bladder and urethra with efferent sympathetic and parasympathetic nerves, respectively, and convey their afferent(sensory)nerves to the spinal cord. The exact cord origin, topographic anatomy, branching pattern and structure of both hypogastric and pelvic nerves vary in different species(Langworthy et al 1940; Baljet and Drukker,1980; Bors and comarr,1970; Bradley and Fletcher,1969;Costa, Furness, 1973; Elbadawi,1980; Elmer,1975; Fletcher and Bradley,1978; Foroglou and Winckler,1973; Gruber,1933; Jayle,1935; Kuntz,1945; Langworthy, 1965; Mitchell,1953; Schnitzlein et al,1972; Sjostrand,1965; Sundin and Dahlstrom,1973; Wozniak and Skowronska,1967). Efferent sympathetic nerves originate T11 to L2 and join the corresponding lumbar chain ganglia; centrifugal branches of these ganglia join the superior hypogastric plexus: a preaortic, lumbosacral, and plexiform nerve arrangement, that gives origin to the right and left hypogastric nerves, each being an elongated plexus. In all other animals studied, branches of lumbar chain ganglia converge on the inferior mesenteric ganglion, located in the root of the colonic mesentery. Well developed in some species, and rudimentary in others(e.g. rat and monkey), this ganglion gives origin to the

two hypogastric nerves, either as a single trunk that shortly bifurcates (rabbit) or two separate trunks(other animals).

The pelvic nerve(nervus erigentis, pelvic splanchnic nerve) conveys efferent parasympathetic nerves, originating in the S2,3,4 to the bladder and urethra. This nerve courses deep in the pelvis, on each side of the rectum, as three to four trunks(man), a double trunk(monkey), or a single trunk(other species).

At a variable distance from target organs, the hypogastric and pelvic nerves of each side meet and branch to form the pelvic plexus(inferior hypogastric plexus, plexus of Frankenhauser). This plexus forms a tridimensional network of freely interconnected nerves in the pelvic fascia, lateral to the rectum, internal genitalia, and lower urinary organs. Divergent branches of the plexus form the posterior rectal plexus, which innervate the corresponding organs.

Afferent vesicourethral nerves are conveyed via the hypogastric nerves to the lumbar, and the pelvic nerves to sacral dorsal columns of the spinal cord. Most sacral afferent fibres reach the cord via dorsal nerve roots, and some via ventral

roots(Ryall and Piercy,1970). Some afferent nerves from urethra-associated striated muscle reach the sacral cord through the pudendal nerves(Kuntz,1945).

- Histochemistry of intrinsic innervation

It is now established that the mammalian bladder and urethra have dual muscular innervation by postganglionic parasympathetic (cholinergic) and postganglionic sympathetic (adrenergic) nerves, with some regional differences in their density and distribution patterns(Elbadawi,1982).In most animal species, the detrusor, base, and urethral muscularis have uniformly rich cholinergic innervation (Elbadawi, 1982,1966,1971,1968). Adrenergic innervation of the vesicourethral smooth muscularis varies regionally, and differently , in various mammals(Elbadawi,1982,1966). In most species, this innervation is virtually absent in the bladder dome, more abundant and more complex in the proximal urethral muscularis than the bladder base, the base than the detrusor, and the outer than the inner parts(Elbadawi,1982,1966,1977, 1974,1968). Neurohistochemical studies on the human bladder and urethra have yielded conflicting observations on the relative density of their dual muscular innervation. One group of investigators reported a uniformly rich cholinergic and

sparse adrenergic innervation of the human bladder in both sexes, with sparse cholinergic and adrenergic innervation of the preprostatic urethral muscularis in the male and the reverse pattern in the female(Gosling et al,1977). No such sex differences, however, have been observed in any animal (Elbadawi,1982,1966;Sundin and Dahlstrom,1973) or in subsequent studies on human organs(Alm,1978; Ek,1977; Kluck,1980; Nording and Christensen,1978).

The adrenergic nerves stimulate both alpha and beta receptors sites in the smooth muscle, the net effect being related to the predominant receptor found in the area. Alpha adrenergic receptor sites are located primarily in the trigone, bladder neck, and proximal portion of the posterior urethra. The beta adrenergic receptor sites are located predominantly in the fundus of the bladder.

The cholinergic receptor sites are located throughout the fundus of the bladder and to a lesser extent in the posterior urethra(Elbadawi and Schenk,1968).

B. Physiology of Micturition

The lower urinary tract has two primary function: adequate

storage capacity and efficient emptying capability. These functions are governed by complex physiologic process that involves several centers within the brain, and the spinal cord. The smooth muscles of the bladder, posterior urethra, and the striated muscle portion of the external urethral sphincter work in a coordinated manner to maintain proper functioning of the lower urinary tract. Micturition is mainly under the control of the autonomic and somatic nervous systems. The former is composed of the sympathetic and parasympathetic nervous systems. The origin of the parasympathetic neural outflow to the bladder, the pelvic nerve, is in the sacral spinal cord; however, the actual organizational centre for the micturition reflex in an intact neural axis is in the brain stem, and the complete neural circuit for normal micturition includes the ascending and descending spinal cord pathways to and from this area and facilitory and inhibitory influence from other parts of the brain. Central nervous system control over lower urinary tract function is less well understood. From the sacral spinal micturition center, the impulses are relayed through the lateral spinothalamic tracts to the thalamus and thence to the cerebral cortex thus bring the sensation of bladder filling to a conscious level. Initially the act of micturition is subconsciously inhibited and later more consciously postponed

by inhibitory impulses blocking the sacral reflex arc. Similarly, noxious stimulation of s2,3 and 4 by trauma to the perineum and anal canal relayed via the pudendal nerve may also be inhibitory and impair the efferent outflow of impulses to the detrusor muscle.

Collecting phase: The sympathetic nervous system exerts an important regulatory influence on bladder function during the filling phase of the micturition cycle by facilitating the storage of urine(Edvardsen,1968a; Khanna,1976). Experimentally, sympathetic effects on lower urinary tract function elicited by filling, or afferent pelvic nerve stimulation, or stimulation of the central stump of the severed sacral root, have been demonstrated and include a depressant effect on intrinsic vesical rhythmicity a depressant effect on the slope of the pressure volume curve, and an excitatory effect on urethral smooth muscular closing activity as well as a depressant effect on ganglionic parasympathetic motor transmission. The filling of the bladder stimulate sympathetic postganglionic innervation to release neurohumoral transmitter norepinephrine which reacts with alpha adrenergic receptors in the bladder neck and posterior urethra, whereby a muscular contraction occurs, increasing the resistance in these areas. When norepinephrine is released at

the beta adrenergic receptors in the fundus of the bladder, relaxation of the muscle occurs. This allows adequate bladder volume at low filling pressures and increases outflow resistance to prevent leakage.

Voiding phase: The voiding phase of micturition is controlled by parasympathetic vesicourethral innervation. When the bladder is distended and maintained at constant volume large rhythmic bladder contractions occurr at frequencies ranging from 0.3 to 6/min depending upon the degree of distention. The parasympathetic neurons are thus active causing a release of neurohumoral transmitter Acetylcholine by the postganglinic nerve cells, which in turn produces a detrusor contraction(Gyermek,1961). It is postulated that at the same time a reflex inhibition of the sympathetic nervous system occurs, causing a reduction in the release of norepinephrine(DeGroat and Saum,1971; DeGroat and Theobold, 1976). This diminishes the alpha adrenergic effect on the trigone, bladder neck, and posterior urethra, resulting in a relaxation of the muscles in this area. In addition, the beta receptor site stimulation in the fundus of the bladder ceases, further enhancing the contractile force generated by the parasympathetic discharge. The net effect is a sustained contraction of the bladder until all the urine is expelled.

Just before a bladder contraction is about to begin, impulses travelling along the pudendal nerve act to relax both the smooth and skeletal sphincter area(Barrington,1914; Kuru,1965). This minimizes the resistance to flow through the urethra and improves emptying efficiency.

C. Basic Urodynamics Knowledge

- Collecting phase

The most important urodynamic parameters to evaluate storage bladder function are detrusor stability.

The bladder wall consists of collagen, elastin, and smooth muscle in addition to epithelium, nerves, and blood vessels. The precise functional relationship between smooth muscle cells and the connective tissue elements is unknown (Coolsaet,1985). It is well known that the muscle cells become elongated during bladder filling. This strain, which is the relative increase in length, decreases the membrane resting potential and increases the frequency of action potentials. Detrusor smooth muscle cells are active during the collecting phase and can even be considered as " pacemaker" cells. Local forces in the detrusor wax and wane during filling, as

reflected in part by undulations on the cystometric curve of subtracted detrusor pressure. Intraluminal pressure changes are normally small for two reasons. First, at any given moment some parts of the detrusor may be contracting while others are relaxing. Second, according to Laplace's law, (p=2T/R), which expresses the influence of the geometry on the relationship between tension(T) and pressure(P), the pressure will only be a partial reflection of the wall forces as determined by the diameter of the bladder lumen[R](Coolsaet,46).

The unstable detrusor is one that is shown objectively to contract, spontaneously or on provocation, during the collecting phase, while the patient is attempting to inhibit micturition. Many terms have been used for this finding. The accepted terms are : "unstable bladder"; "unstable detrusor"; "detrusor instability" and in patients with a proven neuropathy "detrusor hyperreflexia"(ICS,1981). The actual incidence of unstable bladder is unknown. It increases with age so that a majority of the patients over the age of 70 probably have some degree of detrusor instability, but children with enuresis often show detrusor instability as do many women with stress incontinence. The incidence of bladder instability in BPH has been found to be 52-80%(Abram,1985). The classical symptoms produced by the unstable bladder are

those of urgency and urge incontinence. The term instability is defined as the spontaneous or provoked rise in pressure of more than 15 cm H2o(ICS,1980). In some case pressure rises are seen in the absence of detrusor contractions producing a steep cystometrogram known as low compliance. It is debatable whether this is a form of bladder instability as low compliance can be caused by hypersensitive small capacity bladders(e.g. as post-irradiation cystitis) or as an artefact of fast bladder filling during cystometry.

- The Voiding phase

Voiding is initiated by a rapid isometric rise of detrusor pressure(due to the detrusor voiding contraction). Voluntary relaxation of the pelvic floor allows the bladder neck to descend. Urethral pressure is reduced. Following the start of voiding, the urinary flow reaches a maximum rate that is dependent on the intravesical pressure, stimulus of voiding contraction, resistance to urinary outflow, and volume of voided urine. Simultaneous measurements of several parameters are necessary for an understanding as to how the various components of the lower urinary tract interact during this phase.

Maximum Flow Rate(Qmax) The maximum flow rate is one of the most important parameters in urodynamic measurement. Qmax is sex dependent, as it is greater for female than male. Qmax is dependent on volume. It increases as the volume voided increases. The larger the volume voided the greater is the sensitivity for the separation of normal or abnormal voiding (Layton and Drach,1983). The Qmax is also dependent on age. In the normal male, Qmax decreases at a rate of 2 ml/sec for every 10 years of age (Drach et al,1979). However, some authors has found no significant correlation between Qmax and age(Rollema,1981).

Voiding volume Under normal circumstances, maximum flow rate will rise proportionally to the square root of the voided volume - up to a volume determined by the bladder capacity(Layton and Drach,1983). In the case of infravesical obstruction, the maximum flow rate will rise with the volume only to a value determined by the degree of obstruction. The reproducibility and reliability of maximum flow rate is best with voided volumes between 200 and 400 ml. A reduced maximum flow rate obtained at volumes smaller than 100 to 150 ml is considered unreliable.

Flow time in the case of intermittent flow, measurement

of the flow time will be difficult. Post-voiding dribbling is often a non-pathological condition and could affect the true evaluation of the flow time.

Average flow rate(Qave) Average flow rate is derived from the quotient of voided volume and flow time. Average flow rate may incorporate a major degree of uncertainty. This is especially evident if there is intermittency, or terminal dribbling. Mean flow rate has a curvilinear relation to bladder volume.(Kondo et al,1978; Rollema,1981; Susset et al,1973).

Residual urine Normally the bladder contracts fully, and the posterior and anterior urethra coordinate to expel the terminal portion of urine so that almost no urine is left post void. Obstruction affects the normal balance between detrusor contraction and vesical outlet resistance. As the resistance rises and the function of the detrusor muscle deteriorates because of collagen deposition, the bladder is no longer capable of emptying completely. Residual urine is the result of bladder decompensation. Toward the end of urination, the detrusor can no longer maintain sufficient contraction to keep the bladder neck and prostatic urethra open. The stream slows, becomes intermittent, and finally ends in dribbling as the

proximal urethra closes while detrusor contraction fades out, leaving residual urine in the bladder. Many methods are available to determinate residual urine volume. These include isotope scanning, sonography, intravenous urography, and recovery of circulating dye, but insertion of a catheter is the most direct means of measuring the residual urine volume.

Detrusor pressure(Pdet) Pdet is obtained by electronic subtraction of abdominal pressure(Pabd) from intravesical pressure(Pves). It represents the contribution to the intravesical pressure from the stresses in the bladder wall, by both passive and active factors(Griffiths,et al, 1980). In practice, the intra-abdominal pressure cannot be recorded directly. The pressure in the rectum, the stomach, or the prevesical space is taken to be equal to the abdominal pressure. During the slow filling of the bladder the detrusor should normally remain relaxed and the detrusor pressure should rise only slightly. When the patient changes the position or cough the abdominal and intravesical pressure change, but the detrusor pressure remains approximately constant. On the command to void the detrusor contracts actively and raises the detrusor pressure to about 25 cm H2o. The detrusor pressure is maintained with little change as long as flow continues. When the bladder is empty the detrusor

ceases to contract and the detrusor pressure falls close to zero(Griffiths,1980).

Opening pressure(Popen) The passive, perfectly relaxed urethra is closed, and it takes a certain detrusor pressure to open the urethral lumen. Below this pressure the urethral lumen will collapse. The opening pressure is the minimum detrusor pressure to open the bladder neck. In normal male the proximal part of urethra needs higher pressure to unfold than does the rest of the urethra. Once the proximal urethra is opened, urine flows into distal urethra, and exits through the external meatus. The obvious feature of the compressive obstruction such as BPH is that Popen is increased.

Maximum detrusor pressure(Pmax) Pmax is the detrusor pressure measured at peak urinary flow. It is usually used as an important detrusor pressure parameter to express pressure in pressure/flow plots, which is more indicative of the degree of obstruction than flow rate alone.

Isometric detrusor pressure(piso) Piso is the detrusor pressure at zero flow rate, which is obtained by sudden interruption of flow during the voiding process at Qmax. This method was initially described by Gjertsen(1961) and adapted

for the male by Griffiths(1977) and the female by Coolsaet (1980). Detrusor pressure during voiding does not represent the maximal force of the detrusor. This can only be approximated by measurement of Piso. This parameter is an indication for the strength of the detrusor muscle.

Bladder outlet resistance Two sets of calculations of urethral resistance have been used. The first is based on the assumption that the urethra is a rigid tube and should therefore be considered an approximation. Calculation of this resistance factor(R) has the major advantage that it is easily applicable in routine clinical practice. Resistance is calculated from the values of the detrusor pressure at the maximal flow rate(Malkowics et al,1986):

$$R=Pdet/(Qmax)^2$$

An R value of <0.5 cm H2o $ml^{-2}s^2$ is rather arbitrarily considered to be a normal urethral resistance. However, the theoretical basis of using the above-mentioned equation has been questioned as the urethra is not a rigid tube.

The second set of calculations is based on the concept that the urethra is a distensible tube(Schafer,1985). The passive urethral resistance relation(PURR) defines the passive mechanical role of the bladder neck and urethra during

micturition. The urethral opening pressure, Popen, characterising the outlet elasticity and distensibility, can be easily recognized as the pressure where flow starts and ends. Under normal conditions the value for the Popen will be low. The normal pressure/flow rate curve then fits to the following equation:

$$P=Popen + 1/c\ Q^2$$

Where c is a constant factor determined by the computer program using a weighted curve-fitting technique(Schafer, 1983). The normal PURR is defined as a low minimum urethral opening pressure and a concomitant large cross-sectional area as reflected by a steep slope of the PURR. Low Popen and high c values simply reflect an easy-opening urethra that allows high flow rates at low detrusor pressure.

Group-specific urethral resistance factor(URA): The urethra is an active organ that in principle relaxes during voiding, so lowering its resistance to flow. If relaxation is complete, reproducible pressure/flow plots of relatively simple form are obtained(schafer's PURR), which represent the minimum resistance for the urethra in question. If it is incomplete, the pressure/flow plots have complicated, variable forms and urethral resistance is elevated. For a resistance factor to be satisfactory, curves of constant resistance

should follow as nearly as possible the pressure/flow plots found in practice under relaxed conditions. Therefore URA was developed by Griffiths based empirically on the pressure/flow plots recorded in a large number of patients under such conditions(Griffiths,1989). URA can be calculated for any pair of pressure/flow values, the units are the same as the pressure, i.e.cm H2o. URA is thus group specific.

$$URA=[(1+4dQ^2Pdet)^{1/2}-1]/(2dQ^2)$$

Detrusor strength Detrusor pressure during voiding does not represent the maximal force of contraction that the bladder can generate. A contracting detrusor can produce a wide range of different pressures, depending on the rate of urine flow out of the bladder(Griffiths,1980). Thus , during flow, a judgment based purely on the detrusor pressure generated is insufficient. Various methods have been suggested: the stop test(Griffiths,1977; Whiteside,1979; Coosaet,1981), calculation of bladder power(Abrams,1979), plotting of detrusor shortening velocity against detrusor force(Schafer,1983a),or calculation based on the rate of rise of pressure during an isovolumetric detrusor contraction(van Mastrit,1981). The only one of these methods to have come into wider use is the stop test(see isometric detrusor pressure).

From the pressure/flow plots, Griffiths (1989) has expressed the strength of the detrusor contraction (WF) using the detrusor pressure (Pdet), the flow rate(Q) and the bladder volume(V), WF is expressed by the following equation.

$$WF=[(Pdet + a)(Vdet/10 + b) - ab]/2$$

Where: $Vdet= Q/2[3(v + v_t)/4]^{2/3}$

The bladder volume may be calculated from the flow rate curve provided that the volume of residual urine is known. Vdet is an estimate of the shortening velocity of the detrusor circumference. v_t,a and b are constants equal to 10 ml, 25 cm H2o and 6 mm/s respectively. The units of WF are W/m^2 and are related to the mechanical power per surface area of the bladder. Calculation of WF is made from these equations by computer for the whole course of each voiding, and the normal WF corresponding to the peak flow is taken as representative of voiding. The value of WF varies as the strength of detrusor contraction waxes and wanes. During the course of normal, residual free voiding, it rises slowly attaining its maximum value when the bladder is nearly empty. If there is residual urine, it falls prematurely to a low value before the bladder is empty.

D. Urodynamic of Obstruction in BPH

- Flowmetry

Continuous recording of the urinary flow rate during micturition has several clinical advantages. The test is noninvasive and can be performed in privacy. Flowmetry can be used in the hospital, outpatient clinics, and the private office. The flow curve reflects the net outcome of the bladder function and bladder outlet resistance. The presence of infravesical obstruction implies reduction in flow rate and elevation of intravesical pressure. Thus uroflowmetry is applicable as a screening for infravesical obstruction. The maximum flow rate has been the most widely used parameter. A reduction in maximum flow rate-although with great variation-has been a consistent finding in studies of patients with prostatic bladder outlet obstruction(von Garrelts,1958; Rasmussen, Sandoe, and Zachariae,1964; Scott,1967). Von Garrelts(1958) stressed the dependency of the recorded urinary flow rate on the voided volume and overlap in recorded maximum flow rates between patients with prostatic hyperplasia and normal men. He further described the characteristic flow curve

configuration in prostatic hyperplasia as an initial steep rise with subsequent slow decline. The patient with BPH and maximum flow rates of <10 ml/sec usually prove to have infravesical obstruction when assessed subsequently by advanced urodynamic tests. In such patients uroflowmetry is sufficient for documenting infravesical obstruction, and no further urodynamic studies are needed. Patients presenting flow rates between 10 and 15/sec can as well be obstructed as unobstructed.Thus repetitive testing is mandatory in this patient group, and equivocal results indicate a need for further documentation of obstruction before surgery. Patient with maximum flow rate >15 ml/sec rarely have infravesical obstruction, although a small proportion do present with "high-flow high-pressure" infravesical obstruction.

- Cystometry

Several cystometric studies in patients with BPH have shown that detrusor instability is frequent in prostatic infravesical obstruction. The clinical and prognostic significance of obstructive detrusor instability is not clearly documented. Detrusor instability has been shown to be related to aging in obstructed as well as unobstructed patients(Abrams PH 1977), and detrusor instability cannot

always be held responsible for the symptoms of prostatism as instability has been found in more than 50% of healthy elderly males.(Andersen et al 1978). The finding of detrusor instability should not be an indication for prostatectomy.

Evaluation of intravesical pressure in BPH has been a consistent finding in several studies(Rasmussen,1964; Claridge and Shuttleworth,1964; Pierce, Hopkins,and Roberts,1966; Gleason et al,1968; Turner Warwick et al, and Weir,1973). The great variation found in the recorded maximal intravesical pressures has led to questioning the value of this parameter for diagnosis of infravesical obstruction(Castro and Griffiths, 1972). Gleason et al further stated that the detrusor contraction pressure(total intravesical pressure-intraabdominal pressure) appeared to be the most clinically useful voiding parameter, being independent of extraneous influences. Claridge and Shuttleworth(1964) stated three principal changes in detrusor function in infravesical obstruction: a higher resting tonus, a greater contraction force during micturition, and less ability to maintain a constant intravesical pressure during bladder emptying.

- Pressure-flow studies

Since the measurement of bladder pressure and urine flow rate during micturition have become possible from BPH studies, numerous attempts have been made to describe, explain, and define the relationship between the two. In the initial work, the principles of the hydrodynamics of rigid tubes were applied to the urethra and the resistance to flow was calculated as a resistance factor(Smith,1964) or studied as a standard flow (Bryndorf and Sandoe,1960).

The urethra is not a rigid tube. Using urodynamic concepts a theory for steady flow through elastic-walled tubes was developed by Griffiths(1971). He concluded that the normal male urethra contains two constrictions. The proximal constriction near the junction of the prostatic and membraneous urethra determines the flow rate in conjunction with the bladder pressure and energy loss between the bladder and the constriction. The distal constriction near the external meatus controls the velocity of the urine stream for the given flow rate. With the introduction of Griffiths' theory of flow through elastic tubes(Griffiths,1980) it has been shown that the distensibility of the flow controlling zone in the urethra is the major factor determining urethral flow properties, and it became apparent that the use of the resistance factor may be misleading(Bates et al.,1980;Schafer,

1985; Spangberg et al.,1989).

It has been suggested that a plot of detrusor pressure against flow rate throughout micturition should be a useful way of detecting obstruction in BPH(Griffiths,1973; Bates et al,1975). One hundred and seventeen males over the age of 55 were investigated by Abrams and Griffiths(1978) for possible prostatic obstruction. About half of the cases in this series could have been objectively classified as unobstructed or obstructed from the maximum flow rate alone. In about two-thirds of the cases obstruction could be satisfactorily assessed from the maximum flow rate together with the detrusor pressure at maximum flow. In the remaining one-third of the cases, obstruction could be objectively assessed only from a plot of detrusor pressure and flow rate.

In an off-line analysis of clinical urodynamics (pressure/flow) data, Schafer(1983b) showed that bladder outflow obstruction secondary BPH is mainly a compressive type i.e. Characterized by an increase in urethral opening pressure. Griffiths (1989) studying a large number of patients with potentially similar types of urethral obstruction was able to find an empirically based "urethral resistance" factor(URA) which would allow different degrees of "urethral

resistance" to be compared and ranked within the group.

The strength of the detrusor contraction is one of the most important new parameters in evaluation of BPH. If the strength of the detrusor contraction is inadequate, or fades away prematurely, residual urine remains in the bladder(Abrams and Griffiths,1979; Griffiths,1983). In a recent important study, WF and URA were used to evaluate the effectiveness of a trial drug to reduce the size of the prostate in a group of men with obstructed voiding due to BPH. A significant positive correlation between prostate size and URA was noted before treatment. A substantial reduction in the average size of the prostate led to an increase in urinary flow rate and fall in residual urine while on treatment. Surprisingly, however, there was on average no significant change in URA. The strength of the WF increased slightly on average and may have been responsible to the overall improvement in the symptoms (Griffiths,1989).

OBJECTIVE OF THE STUDY

The overall objectives of this study were:

1. To establish a suitable animal model in which urodynamic studies can be done physiologically. The animal model should fit the following criteria: 1) awake state, 2) natural upright position, 3) no urethral catheter or instrumentation, 4) simultaneous measurement of urinary flow, bladder pressure, abdominal pressure with access for stoppage of voiding, to measure isometric bladder pressure(Piso), 5) potential for applying an artificial sphincter cuff around the bladder neck to maintain a partial obstruction that can be reversed.

2. To apply the standardized model in young adult animals: 1) To define the normal baseline urodynamic profiles. 2) To define the functional urodynamic changes following obstruction. 3) To define reversibility of urodynamic changes following relief of the obstruction.

EXPERIMENTAL DESIGN

A. Animal Choice

The following guidelines were observed in this regard: 1. similarity of its lower urinary tract anatomy and innervation to the human; 2) reasonable tolerance to standard general anesthetics; 3) large size urethra to allow placement of the artificial sphincter; 4) reasonable rate of operative, early postoperative, and long-term natural attrition; 5) amenability to repeated handling without anesthesia for long-term follow-up urodynamic evaluations; and 6) adherence to ethical, emotional and human principles governing the use of animals for biomedical research.

The rat does not qualify for this study because of the very small size of its urethra and bladder that prohibits the application of the obstructive device, and the difficulty of in vivo urodynamic studies. The rabbit also does not qualify, despite the adequate size of its organs, because of its known timidity, fragility, poor tolerance to anesthesia, and susceptibility to systemic and urinary tract infection resulting in an unacceptably high attrition rate(>30%) in long-term experiments. Although cats are costly to purchase

and maintain, they have a finicky nature that would eliminate successful repeated urodynamic studies without anesthesia. The dog would be perfectly suitable from the experimental viewpoint, but was eliminated because of emotional humane reasons. The pig was chosen as a perfectly suitable alternative.

The Female Yucatan Microswine, reaching sexual maturity at the age of 5-6 months with a 20-30 kilogram body weight, and a 40-60 kilogram weight at 12-14 months of age, was used in this study; the adult size and weight would allow relatively easy handling of the animal for repeated in vivo urodynamic studies.

B. Access for Pressure Measurement of Bladder and Abdominal Cavity

One of the most difficult problem encountered during urodynamic study evaluation in awake animal is access to the bladder for the measurement of bladder pressure, without external manipulation of urethra i.e. catheters. This was accomplished by the use of portcatheters(Fig.1), the catheter ends of which were implanted into the bladder and peritoneal cavity, and the ports placed under the skin of the back for

easy cannulation. The microport is a totally implantable device which has been designed and used to provide repeated access to the vascular system or selected body sites in humans without the trauma associated with multiple punctures. The system consists of self-sealing injection port and a radiopaque catheter for blood sampling or the delivery of medications, nutritional and imaging solutions. Access to the port is obtained by percutaneous needle insertion. The portcatheters have been used in our experiments and have been found suitable for bladder and abdominal cavity pressure measurement and bladder imaging examination.

C. Creating Obstruction

The basic aim of the model was to create a mechanical barrier to 'expansion' and not actual constriction of the bladder outlet during voiding. Such a barrier should be easy to install and remove. It should be inert biologically, to obviate complicating local tissue reactions in long-term experiments. Based on previous experience in human, the 4.5 cm American Medical Systems inflatable sphincter cuff(Fig.2) was chosen and used in this project.

D. Urodynamic Studies

Urodynamic studies(Fig.3) were performed in each animal according to the following protocol:

Baseline studies With the portacath in place, before placement of the obstructive device, three urodynamic studies were carried out to establish baseline profiles.

Obstructed With the artificial sphincter cuff implantation, the animal had follow-up urodynamic studies every month for the duration of obstruction.

Relief the obstruction Repeated urodynamic studies were carried out monthly on the first postoperative month, at the end of the second, and at the end of the third.

Urodynamic study equipment Two equipments were used. DISA 2100 URO System was used for the study of the collecting phase. R.L. Medical UDS-120 Urodynamic Analyzer was used for measurement of the voiding phase. UDS-120 Urodynamic Analyzer is a urological data acquisition system produced by Laborie Surgical Ltd.(Toronto). It measures and digitally stores uro-flow, volume and pressure information data. It is comprised of three major sections: computer(IBM PC 386), UDS-54 urodynamic analyzer, and printer. The volume transducer produces a

signal by measuring the weight of the urine voided. The flow is determined by differentiating the volume signal with respect to time. All of the pressure/flow information from studies are stored in the computer, and can be plotted and analyzed for the measurement of pressure/flow relationship and calculating the various parameters i.e.urethral resistance and bladder strength.

DISA 2100 URO System consist of 21K04 Weight Transducer, 21H04 H2o Pump, 21C15 Manometers, 21C10 Mictiometer,21E01 Cystometer Unit, 21E03 H2o Control Unit,and 21K02 Uroflow Transducer. The flow rate of the infusion liquid is calculated by differentiation of the Weight Transducer signal. The flow rate measured is displayed in ml/min. The bladder pressure and abdominal pressure are picked up via two 21C15 Manometers, and the detrusor(bladder pressure minus abdominal pressure) is shown on the display. The volume infused into the bladder is measured by the 21K04 Weight transducer and displayed in ml. With a 21C10 Mictiometer incorporated in URO System, the volume voided will automatically be subtracted from the volume infused. The bladder compliance is read in ml/cm H2o and is calculated from volume increase divided by pressure increase.

MATERIAL AND METHOD

A total of thirty-one Female Yucatan microswine minipigs aged 4-8 months with a mean weight of 21.8 Kg(range 11 -43 Kg) were studied. The animals were divided into two groups, 21 pigs as obstructed group, and 10 as control. All animals had routine blood work done including blood urea nitrogen, creatinine, and urine cultures every month.

A. Radiological studies

The animals were anaesthetized with Ketamine(20 mg/Kg) and maintained by Pentothal. For voiding cystourethrography (VCUG), The pigs were placed in lateral position on X-ray table. Reno-m-60 was diluted to 1/10 its concentration and used as contrast medium. The contrast was infused through the right portacach to the bladder by gravity at 70 cm height. One to two films were taken during voiding. The prone position was used for IVP. Reno-m-60 was injected intravenously at a concentration of 1 ml/Kg body weight. Films were exposed at 5,15 and 30 minutes after injection.

B. Biochemical and Urine bacteriology

Urine specimens were obtained for culture at start of the experiment by direct bladder puncture at operation, and later specimens was obtained by aspiration via the portacath at the time of urodynamic examination. Urine culture was repeated every 2-7 days when the pig had infection.

C. Surgical Preparation

The pigs were fasted 12 hour before surgical and x-ray examination. Premedication with Atropine 0.04 mg/Kg i.m. was injected. The pigs were sedated with an IM injection of Ketamine 20 mg per kg. A suitable vein on the ear was cannulated to establish intravenous access. Ten cc of 2.5% Pentothal was then injected i.v. for induction. The Pentothal was repeated during x-ray examinations and the aesthesia was maintained by inhalation of a mixture of Halothane(1.0-1.5%), Oxygen(2L/min) and Nitrous Oxide(800-1000ml/min.) for surgical operations. The animal breathed spontaneously. Trimethoprim/sulfa 2.2 mg/Kg was given i.m. prior to the surgery to prevent infection.

D. Implantation of the port-catheters

Microport(Shiley Infusaid, INC.) with radiopacque

silicone rubber catheter(O.D. 3.3 mm I.D. 2.0 mm) was used in this study.

The pigs were placed in prone position. A 5 cm midline back incision was made at the L2-L4 level and then two pockets were created under the skin of each side of the incision to accommodate the portacath reservoir. A 60 cm length of tubing was threaded subcutaneously on each side of the abdomen and left under the skin of the lower abdomen for later easy identification. The skin of the back was then closed. The pigs were then put in the supine position, the bladder exposed through a midline abdominal incision and a pursestring suture placed at dome of the bladder. The two portacath tubings already implanted were then identified in the incision and were threaded throug the abdominal wall to reach the bladder and peritoneum. The right side tubing was cut so that 5 cm length could lie within the bladder. Three to five lateral holes were made in the end segment and then inserted into the pursestring suture. The suture was then tied around the tubing to render the bladder watertight. The bladder dome was fixed to the abdominal wall fascia with two 3/0 chromic catgut sutures on each side of the catheter to prevent its displacement(Fig.4). For the assessment of the collecting phase, in 9 animals, two portacath were implanted on the right

side, one for infusion, and the other for monitoring intravesical pressure. The left side portacath tubing was prepared in the same way and left lying free in the Pouch of Douglas. The incision was then closed in layers.

E. Implantation of the Artificial Sphincter

The pigs were placed in supine position after anaesthesia and a 10 cm midline low abdominal incision was made. The bladder neck was explored and the urethra was dissected very carefully to avoid injury of related nerves and blood vessels. The circumference of the urethra was measured using a measuring tape. A 4.5 cm artificial sphincter cuff(American Medical system Sphincter 800^{TM} Urinary Prosthesis) deflated was applied loosely around the urethra and snapped into position(Fig.5). The open end of the cuff tube was plugged using a metal pin and threaded subcutaneously, placed under the skin. The wound was closed in layers and dressed.

For the control sham group(6 animals), the operation was carried out as described, however, the artificial sphincter cuff was taken out before the wound was closed.

F. Relief of infravesical obstruction

Under general anaesthesia and aseptic condition via a small abdominal incision, the bladder neck was gently explored. the artificial sphincter cuff was unbuttoned and removed in-toto. the wound was closed in layers.

G. postoperative care

The pigs were moved to the recovery room after operation. Supplemental heating was used by light until the pig recovered from anaesthesia. The animals were housed separately for 5 days. Antibiotics were given whenever a positive culture was obtained according to sensitivity testing. The following antibiotic agents have been used when necessary: Amikacin 10 mg/Kg b.i.d., Nitrofurantoine 4.0 mg/Kg b.i.d., Tribrissen^{480} 2.2mg/Kg b.i.d., and Keflex 30 mg/Kg b.i.d., Nitrofurazone was used for flushing portcatheters. Trimethoprim/Sulfa 2.2 mg/Kg b.i.d. was given postoperatively for 5 days to prevent infection.

H. Urodynamic studies

The performance of urodynamic studies in the awake animals necessitated the construction of a cage and sling to immobilise the animal in the upright posture.

- The Restricting Cage

The cage consists of three solid transparent plexi-glass measuring 120 cm long and 90 cm high. The base piece is mounted on four small lockable wheels for easy mobility. Each side wall has a total of 43 holes opposite each other designed to allow aluminum rods to pass through in order to prevent the animal from moving forward and backwards (Fig.6). The holes also provide air circulation around the animal to prevent overheating. One of the side walls is fixed and the other adjustable to allow easy use for the different sized animals. A specially designed sling(Fig.7) with four holes to receive the upper and lower limbs of the animals is suspended inside the cage to keep the pig comfortably in the erect posture. This was designed again to reduce the animal mobility, and allow for voiding in a flowmeter in the erect position. It also allow easy access to the meatus for stopping the flow during the last voiding cycle. the cage was designed in the biomedical engineering laboratory of McGill university.

The animals adapted very well to the restraining cage, although we had to modify the design of the original cage. Transverse solid aluminum bars were incorporated into the base of the cage to prevent breakage. A rubber pad was installed on

the base plexi-glass plate to prevent the animal from sliding. During the initial study period, the animals had a tendency to lie down necessitating construction of an adjustable moving up and down sling to hold the animal in the upright posture(Fig.8).

- Urodynamic evaluation

Urodynamic studies were carried out using two different techniques:

1) evaluation of the collecting phase.

In the early studies, evaluation of the collecting phase could not be carried out while the animal was awake because of the numerous artifacts from movement of pigs. These artifacts were abolished when Ketamine sedation was used. Thus Ketamine sedation were used for evaluation of the collecting phase. A slow normal saline infusion via a y-connector through the abdominal port-catheter was used when it's pressure was not measured well.

2) evaluation of the voiding phase.

This was carried out while the animal was not sedated within the cage in the upright posture;

Evaluation of collecting phase Nine animals(include 4 control) were used for collecting phase study to measure bladder stability and compliance .

The animals were sedated by injection of 20 mg Ketamine per Kilogram body weight. After 5 to 10 minutes, the pigs were then moved in a sling awake but sedated. DISA urodynamic equipment was used. The port-caths from abdominal cavity and bladder were connected via pressure transducer to measure abdominal and vesical pressure respectively. Warm 0.9% Saline(37 degree centigrade) was infused via the third portcath into the bladder at 15 cc per minutes.

Evaluation of the voiding phase Twenty-two pig(including 6 control) were used for the voiding phase.

The awake animal was gently encouraged to walk into the specially designed restraining cage. The animals' limbs were introduced into their respective openings in the sling. With the manual outward rotation of the pulleys attached to the end of the sling, the sling was gently elevated raising the animal high enough to maintain the animal in the upright posture. Sufficient backward leverage is allowed to enable the animal to squat immediately above the urinary flow meter during micturition. The back skin covering the portacath reservoir was anethetized using 5% Pralocaine cream(Astra Pharma Inc.). After 15 minutes, the portacath site on the back of the pig were cleaned with iodine soap, rinsed and iodine applied

directly to sterilize sites prior to puncturing. A 20 gauge 1 1/2 in. needle(2/3 of it curved at 90 degree) was inserted into the vesical port-cath reservoir. The needles in both portacaths were then connected to a 100 cm long F5 tubing to external H_2o transducer and UDS-120 Urodynamics Analyzer (R.laborie Medical Corp.). The total bladder pressure and intra-abdominal pressure were measured. A flow meter was placed behind and underneath the animal to measure uroflow and voiding volume. Diuresis was induced by 5% Furosemide(2.2 mg/Kg i.m.), 3 to 4 voiding cycles were obtained. Isometric pressure was obtained in the last voiding by manual interruption of flow per vaginum.

Analysis of data

1. Urodynamic Parameters

The following urodynamic parameters were measured:

Collecting phase

detrusor instability: a pressure rise exceeding 15 cm H_20 during the collecting phase was an indicator of detrusor instability.

Voiding phase

Popen: the opening pressure, i.e. the detrusor pressure needed to open the urethra at the start of voiding.

Pdet: detrusor pressure obtained by subtraction of abdominal from intravesical pressure(the value of Pdet in this paper refers to the maximal detrusor pressure).

Pmax: the detrusor pressure measured at peak urinary flow.

Piso: maximal detrusor pressure was determined by manual interruption of flow in the voiding process at Qmax.

Qmax: the maximum flow rate.

Average flow: the quotient of voiding volume and total voiding time.

Flow time: a period between the urine flow start and end.

Voiding volume: total urine collected from a voiding.

Residual: This was measured by directly withdrawing urine from right port-cath after voiding.

2. X-Y plots analysis

The flow (Q) and Pdet were plotted on an x-y recorder to evaluate the pressure flow relationship.

Bladder outlet resistance Bladder outlet resistance was evaluated by calculation of the resistance factor(R), Passive urethral resistance relation(PURR) and Group-specific urethral resistance factor(URA). The R is based on the assumption that the urethra is a rigid tube and should therefore be considered an approximation. The passive urethral resistance relation(PURR) and Group-specific urethral resistance factor(URA) are based on the concept that the urethra is a distensible tube.

Detrusor strength Two parameters were used to evaluate the detrusor strength: isometric detrusor pressure(Piso) and WF. Piso was obtained during a stopflow study. WF was calculated using the Griffiths and Van Mastrigt formula, which quantified voiding detrusor contraction by a combination of the detrusor pressure, the flow rate, and the volume in the bladder.

I. Statistical Methods

T-test was used to examine the statistical significance of urodynamic parameters between two groups. For comparison of more than two groups, one-way analysis of variance was used. The significant level was set at 0.05. Person correlation

Coefficient(r) was used to assess the strength of association between the parameters. r value close to 1 is considered as positive association.

RESULTS

Implantation of the port-catheters were carried out in all animals. The animals tolerated the port-catheters very well and none were rejected or infected. The pig's mean urethral circumference was 2.42±0.33 cm. The circumference of artificial sphincter was 4.5 cm so that there was ample room between the cuff and urethra.

A. Radiology

Twenty-one normal minipigs had successful IVP and VCUG examinations. One animal had an allergic reaction to the contrast medium used. All of the animals showed a normal IVP(Fig.9). Thirteen pigs (62%) had Grade I to Grade II reflux(Fig.10). Twelve animals had reflux on both sides and eight had no reflux. The reflux occurred in the young animals.

B. Urine Bacteriology

Urine cultures were repeated every week following surgery in all pigs. A bacterial growth exceeding 10^5 colonies/ml of E.Coli was found in 13% of the animals and 4% had Staph Aureus.

C. Urodynamic studies

Three-hundred sixty eight urodynamic studies were done. Forty-six for the collecting phase studies, which included 20 baseline studies, 18 obstructed and 8 studies following removal of the sphincter cuff. In 302 voiding phase studies, 115 were baseline, 144 obstructed and 43 after the relief of the obstruction.

- Collecting Phase

Figure 11 shows numerous artifacts during the collecting phase. This was secondary to the animals sudden movements and gruntings which were transmitted via the subcutaneously implanted silastic tubings of the port-catheters. Following Ketamine sedation, all artifacts were abolished(Fig.12) and thus evaluation of this phase was accomplised using Ketamine.

Bladder instability was found in one animal(11%), which had a higher than 15 cm H20 contraction before voiding. The other eight animals had no bladder instability.

After 4 weeks obstruction, 4 of 5 Pigs demonstrated

bladder instability(Fig.13). The contraction usually occurred just before voiding. The control group had stable bladders. After relief of obstruction, bladder instability could not be demonstrated in all 4 animals.

- Voiding Phase

1. Baseline study

Twenty-two minipigs completed baseline urodynamic evaluations. A total of 115 studies were performed, 71 normal pressure flow studies and 44 isometric detrusor pressure studies. Sixty-five studies were excluded because the voided urinary volume was less than 100 ml(occurred in the initial stage), failure of the Pabd measurement due to obstruction of the tubing and inability to obtain Piso(either because the detrusor pressure decreased or the recorded value was not obtained).

Thus, 50 complete studies, 28 normal pressure/flow and 22 isometric pressure studies were considered adequate and are used for the analysis during this study.

A normal voiding pattern was noted in all animals. There

was an initial rise in intravesical pressure and at Popen, the urinary flow began. This was achieved by continuous detrusor contraction during which the intravesical pressure remained relatively constant until the bladder was empty when flow ceased and Pdet returned to baseline (Fig.14).

Mean voiding volume was 179.8 ±71 cc in the normal pigs. It was correlated with the body weight, as the voiding volume was higher in animals of larger size. There was also a clear relationship between urine flow and the voiding volume, Qmax was low in lower voiding volumes(Fig.15).

The mean maximum flow rate was 20.5±6.6 ml/sec with 12.7±4.3 ml average flow rate. The mean flow time was 15.9±7.0 second(Table 1).

Detrusor pressure was relatively constant in all animal studies, with Popen mean of 19.9±8.1 cm H_2O; Pmax mean 15.7±6.7 cm H_2O and Pdet mean 34.2±10.8 cm H_2O(Table 2). The isometric detrusor pressure, Piso was 51.6±11.0 cm H_2O(Fig.16)

The pressure flow relationship in all animals was noted to be in the low pressure and high flow range, typical of normal voiding with no obstruction(Fig.17). The urethral

resistance was quantified using R,PURR, and URA obtained from the pressure/flow plot. The R value in normal pigs was lower than 0.5 cm $H_2oml^{-2}.s^2$ and has a range from 0.01 to 0.28. The PURR was located on the left side of the curve with a lower Popen and high flow. The normal URA has been noted to be lower than 10 cm H2o(Fig.18). The mean URA for the entire group was 7±2.7 cm H2o with a range of 1-13 cm H2o(Fig.19).

The plot of WF against bladder volume showed a sharp increase of WF in conjunction with the detrusor contraction. Following a short peak, it fell to baseline as the bladder emptied(Fig.20). The average WF was 3.9±1.0 w/m^2 with a range of 2.1±5.7 w/m^2(Tab.3)

2. Obstruction and Deobstruction

Urinary Flow (Q):

In the normal control, Qmax remained stable with a mean of 30.8±9.2 ml/s during the 12-week study period. In the experimental obstructed group, there was a progressive reduction in Qmax from the baseline mean of 20.5 ml/s to 5.6 ml/s at 12 weeks post-obstruction($p<0.004$). This was associated with an increase in the flow time($p<0.03$). The

flow parameters are shown in Table 4. Following 12 week de-obstruction, mean Qmax was 25.0±9.7 ml/s with 13.0±3.6 average flow, the flow time decreased to the normal. The voided volume in the two groups is compared in Table 5. In the experimental obstructed group, the voided volume was reduced from the baseline volume of 179.8 ml to 102.4 ml at 12 weeks post-obstruction(Fig.21). Mean voiding volume increased to 219.1±119 ml after 12 weeks of removal of obstruction.

Residual urine gradually increased. Mean residual increased to 124.6±193.6 ml (range 10-540 ml) at 8 weeks of obstruction and 365.0±305.9 ml at 12 weeks of obstruction($p<0.018$). After 12 weeks all the pigs, except one, had more than 100 ml residual urine. Residual in the control group remained low. The mean value was 14±10.4 ml (range 0-29 ml) at 12 weeks post- operation. After 12 weeks from removal of obstruction, the mean residual decreased to 47.2±41.9 ml.

Detrusor Pressure:

The pressure parameters are shown in Table 6. There was a progressive increase in detrusor pressures (Fig.22) in the

obstructive group in relation to the time and duration of obstruction. At 12 weeks of obstruction, although Popen was still increasing, both Pmax and Piso have already reached their peak. At that time, there was a 4-fold increase in Popen($p<0.008$), 6-fold increase in Pmax($p<0.02$) and 3-fold increase in Piso($p<0.01$)(Fig.23). By the third month following release of obstruction, the Popen, Pmax and Piso had returned to 70%, 88% and 93% respectively of their pre-obstructive value(Fig.24,25,26). The composite changes in the detrusor pressure are illustrated in Fig.27.

Pressure/Flow Relationship:

There was a marked difference in the pressure/flow relationship between the two groups as depicted in Fig.28. The normal sham group had their pressure flow plot in the high flow and low pressure region of the graph whereas the obstructed group in the upper left corner of the graph which was located in high pressure and low flow district. This feature is well represented in Fig.29.

Urethral Resistance:

Urethral resistance(R) Two weeks after obstruction, the

mean R value had increased to 0.59 cm H2o ml^{-2} s^2. By the end of 12 weeks obstruction, The R value was increased to 26.89 cm H2o $ml^{-2}s_2$, while the control group remained under 0.5 level. All of the R values returned to normal under 0.5 except in one animal at 4 weeks of relief the obstruction. The mean R value was 0.1 at 12 weeks of relief of the cuff(Fig.30).

Passive Urethral resistance relation(PURR) Popen gradually increased and Qmax decreased with obstruction. The PURR shifted to high pressure over time after obstruction(Fig.31). At 12 weeks obstruction, the Popen reached 85.2 cm H2o, the Qmax was 5.6 ml where the Pdet was measured at to 85.7 cm H_2o. The PURR in control group fluctuated within a narrow range 4-12 weeks postoperation, with 22.3 cm H_2o of lower Popen and 30.8 ml/sec of higher Qmax with 30.8-39.5 cm H2o of detrusor pressure.

PURR returned toward normal after 12 weeks of relief of the obstruction, the Popen was 39.9 cm H2o, Qmax was 25.0 ml/sec with 47.3 cm H2o Pdet.

Urethral Resistance Factor The URA was under 10 cm H_20 in the baseline study. URA remained stable throughout the study period in the control animals, whereas in the

experimental group, it increased 10-fold compared with baseline. There was a parallel increase(r=0.83) between URA and Popen. Comparison of URA and Popen in both groups is represented in Fig.32. After relief of obstruction, URA reverted to normal by the 12th week (Fig.33).

Detrusor Contractility WF:

Detrusor contractility or the power factor WF increased progressively with the duration of obstruction. There was a 3-fold increase in detrusor contractility by the 12th week of obstruction (Fig.34). In comparison in the normal control group, WF remained stable throughout the study period(table 7). Comparison of WF with Piso in relationship with the duration of obstruction is shown in Fig.35. There was a parallel increase between the WF and Piso(r=0.94). Following release of obstruction, there was a decline of WF with Piso. The changes with obstruction and following relief of obstruction are depicted in Fig.36.

DISCUSSION

Advantages of the animal model

The most interesting feature of this model is that urodynamic studies can be done in the conscious state and normal upright posture. Subcutaneously implanted port-catheters make it possible to establish the access for both the bladder and peritoneal cavity for the measurement of total bladder pressure and abdominal pressure respectively during bladder storage and micturition. The success of urodynamic study was also due to the design of a suitable restraining cage so that the urinary flow rate can be simultaneously determined. The method of using port-catheters for access to the bladder and peritoneal cavity has never been previously reported. The animals tolerated silastic material well throughout the study period and catheters kinks did not occur even with normal growth of the animals. The incidence of urinary infection was reasonably low, and once established, treatment was easily accomplished. Port-catheter access by needling was easily accomplished by the prior use of local anaesthetic cream. During the initial study period, the abdominal pressure was measured by a balloon catheter inserted into the rectum. This was found

impractical and unreliable as the animals could not tolerate the balloon and thus expelled it. The modification using port-catheter with direct access to the peritoneal cavity has proved successful. Using a slow normal saline infusion via a Y-connector through the port-catheter has increased the sensitivity of the abdominal pressure measurement, by eliminating obstruction to the intraperitoneal tubing.

Bladder outlet obstruction using an artificial urinary sphincter cuff(AMS 800) size 4.5 cm was created in all experimental animals. In the previous studies, sutures or rings were used to produce bladder outlet obstruction, the obstruction was obtained by directly decreasing the diameter of urethra like a urethral stenosis. The implantation of a silastic cuff surrounding the posterior urethra and not compressing it allowed us to simply prevent the expansion of the posterior urethra (bladder neck funnelling) and prevented full opening of the urethra during voiding. Therefore the obstruction was closer to the effects produced in man by BPH. The Inflation of the cuff with fluids to create obstruction was not necessary. The obstruction was very gradual until the 12th to 16th week of obstruction when all animals had large residual urines. Since the pigs had similar urethral circumference(mean value 2.42±0.33 cm),and we used the same

which is quite similar to the Guinea pig study (Mostwin et al, 1991). However, we can not prove that the short duration of bladder instability was the only reason accounting for reversibility. Arnold(1980) has pointed out there is little correlation between the duration of obstruction and reversibility of detrusor instability.

Urinary infection was found in 17% of pigs during the studies. The presence of infection did not appear to be causally related to the development of detrusor instability. In addition, infection was present in many of the obstructed pigs studied by Hodson et al(1975)(54% infected) and Ransley and Risdon(1978)(47% infected), yet none of these animals had unstable cystometrograms. Sibley(1985) reported that the incidence of urinary infection in obstructed animals was 47%. He did not believe it was related to bladder instability.

In the voiding phase, the obstructed model presented the changes of a low flow rate similar to previous studies in humans. Guidelines for the diagnostic value of recording maximum flow rate in the absence of primary bladder dysfunction have been given by Abrams and Griffiths(1979): patients with BPH and maximum flow rates of <10 ml/sec usually prove to have infravesical obstruction. If the maximum flow

rate is greater than 15 ml/sec, patients rarely have infravesical obstruction. Using these criteria in our 45 obstructive studies, 73% had maximum flow rate lower than 10 ml/sec, whereas in 51 baseline and control group studies, 87% had maximum flow rate higher than 15 ml/sec and 96% higher than 10 ml/sec.

The detrusor pressure recording were characterized by typical obstructive urodynamic parameters. All detrusor pressures (Popen, Pmax, Piso) increased progressively with the duration of obstruction. By 12th week of obstruction, all animals were carrying residual urine and the detrusor pressures had peaked. This point in time appears to correlate with the change from detrusor compensation to decompensation. The increasing Popen and Pmax are in agreement with findings in man with BPH. The study shows that the feature of obstruction was characterized by increased Popen and Pmax. In the control, although the Popen and Pmax pressure fluctuated, there was no more than 50% pressure change. Kato(1990) has shown the same result in which the voiding pressure increased by at least 50% in the obstructed cats. Piso in the normal males has been found to be 60 cm H_2O. It was found to be 100 cm H_2O in a group of patients with prostatic obstruction(Susset,1983). This is also similar to

our present study.

We have obtained that Qmax and Piso revert to the control level after relief of the obstruction by 12 weeks, however, both Popen and Pmax recovery to control level is not as certain. This is probably related to detrusor structure change.

The urethral resistance changes were very similar to human. An R value of <0.5 cm H2o $ml^{-2}s^{2}$ may also be considered as normal pigs for urethral resistance. URA was developed based empirically on the pressure/flow plots recorded in a large number of patients. It could be used in this study because pigs have the same obstructive features(high pressure, low flow). The statistical significant difference ($p<0.018$) between normal and obstructed animals further proved that URA can rank different voidings according to the animals urethral resistance changes. Since URA is related to Popen, there was a marked parallel correlation of the two during the period of the study. The bladder strength were evaluated by both Piso and WF. The detrusor contractility behaved in unison in the entire studies. In practice, the Piso could not be obtained in half of the studies, and it caused animal discomfort and increased the incidence of invaluable studies. We feel that WF

WF is more reliable for measurement of detrusor contraction strength.

The present model has been developed and has proved to be ideal for studying the urodynamic changes, and their reversibility following and after relief of obstruction. The preliminary experiments done demonstrate the similarity of this model to other infravesical obstruction in man.

CONCLUSIONS

A minipig model has been developed to measure pressure/ flow relationships in the conscious state and natural posture. This was obtained by subcutaneously implanted portcatheters to the bladder and peritoneal cavity and by the use of the restraining cage and sling. Obstructive urodynamic profile have been achieved by using an artificial sphincter cuff placed around the bladder neck; not to compress the urethra but to prevent bladder neck expansion during voiding.

The collecting phase study was carried out under Ketamine sedation to abolish movement artifacts that interfered with the bladder pressure tracings. There were a decrease in compliance and development of bladder instability in the one month obstructed animals which reverted to normal following 4 weeks removal of obstruction.

The voiding phase was carried out in upright conscious minipigs. Low bladder pressure and high flow rate were normal; Progressive pressure increase and decrease of flow rate was noted with obstruction; Following 3 month relief of obstruction, Qmax reverted to pre-obstructive level whereas Popen, Pmax, and Piso were decreased to near their pre-obstructive levels.

TABLE 1

Minipigs' Flow Parameters (37 Studies)

Qmax (ml/sec)	Average Flow (ml/sec)	Flow Time (sec)	Volume (ml)	Residual (ml)
27	18	8	168	
24	10	15	164	17
14	9	16	155	0
17	9	13	125	
11	7	16		
14	6	33	285	
22	15	17	258	0
24	11	21	246	
26	12	28	340	
26	12	18	230	0
24	21	15	320	
33	16	23	254	34
23	15	9	141	
23	17	16	285	
27	18	17	316	39
17	12	11	137	
16	12	16	199	
28	20	9	180	
13	8	13	113	
17	10	12	129	
22	7	13	117	27
17	9	17	137	6
23	7	37	195	
10	9	27	102	
31	18	7	129	
20	9	20	199	
8	7	16	113	
9	19	22	117	
17	11	11	113	
26				
27	14	15	215	
30	19	13	254	16
20	11	13	145	
24	15	8	125	
23	17	7	125	
18	10	10	109	
16	12	10	121	4
Mean 20.5	12.7	15.9	179.8	14.3
SD 6.6	4.3	7.0	70.5	14.8

Table 2

Pressure Studies (34 Studies)
(cm H_2O)

	Popen	Pmax	Pdet	Piso
	16	11	33	36
	18	10	34	59
	16	13	21	30
	15	18	45	64
				49
				61
	0	7	55	
	12	19	58	65
	19	13	21	
	21	16	24	
	21	9	21	50
	8	10	23	50
	23	21	56	
	32	21	32	53
	31	22	32	
	29	15	37	
	23	15	25	53
	35	25	39	48
	22	10	33	
	28	21	31	35
				57
	14	8	30	
	12	19	36	
				50
	11	1	23	58
	21	30	31	41
				78
	28	23	32	
	20	27	36	
	19	9	19	
	13	14	47	57
				43
	18	13	44	55
	32	19	39	44
Mean	19.9	15.7	34.2	51.6
SD	8.1	6.7	10.8	11.0

Table 3. Resistance and Strength of Bladder Contraction In Normal Pigs

(29 Studies)

	URA (cm H_2O)	WF (w/mm^2)
Mean	7	3.9
SD	2.7	1.0

Table 4. Comparison of flow parameters in two groups

	Control			Obstructed		
	Qmax ml/s	A.F. sec.	F.T. sec.	Qmax ml/sec.	A.F. sec.	F.T. sec.
B.S.	20.5	12.7	15.9	20.5	12.7	15.9
2w	28.4	17.4	13.0	13.0	8.5	22.5
4w	31.4	19.2	11.8	13.5	8.9	23.0
8w	30.3	13.0	12.7	9.1	5.4	72.2
12w	30.8	15.5	15.8	5.6	1.9	100.6
	Control			de-obstructed		
1m	30.8	15.5	15.8	19.7	10.0	8.6
2m	33.8	18.4	20.0	23.1	9.7	14.4
3m	30.8	10.0	31.7	25	13.0	16.1

B.S.=Baseline W=Week m=month
A.F.=Average flow F.T.=Flow time

Table 5. Comparison of bladder Capacity in two groups

	Control		Obstructed	
	Volume ml	Residual ml	Volume ml	Residual ml
B.S.	179.8	14.3	179.8	14.3
2w	243.8	11.3	176.9	72.7
4w	214.0	14.2	170.8	27.5
8w	208.5	19.5	144.2	124.6
12w	264.2	14.0	102.4	365.0
	Control		De-obstructed	
1m	264.2	14.0	92.1	29.7
2m	220.4	44.2	172.3	35.9
3m	305.8	28.3	219.1	47.2

Table 6. Changes in Detrusor pressures

	Control			Obstructed		
	Popen cmH_2o	Pmax cmH_2o	Piso cmH_2o	Popen cmH_2o	Pmax cmH_2o	Piso cmH_2o
B.S.	19.4	16.4	51.4	19.4	16.4	51.4
2w	19.4	22.2	60.8	34.1	37.7	64.0
4w	22.6	16.8	52.2	44.3	49.9	73.2
8w	20.5	12.2	65.0	59.3	66.1	88.2
12w	28.8	22.5	61.7	85.2	94.4	135.2
	Control			De-obstructed		
1m	28.8	22.5	61.7	28.9	16.0	62.0
2m	31.8	17.6	59.2	39.1	28.3	61.1
3m	22.3	14.0	52.3	39.9	25.9	58.0

Popen=opening detrusor pressure
Pmax=detrusor pressure at maximum flow
Piso=isometric detrusor pressure

Table 7. Comparison of URA and WF in two groups pigs

	Control		Obstructed	
	URA cmH_2o	WF W/mm^2	URA cmH_2o	WF W/mm^2
B.S	7.1	3.9	7.1	3.9
2w	12.3	3.9	18.0	5.6
4w	5.5	4.3	16.5	7.7
8w	5.1	3.8	37.9	8.1
12w	7.7	4.7	74.3	13.3
	Control		De-obstructed	
1m	7.7	4.7	7.9	5.3
2m	5.2	4.0	10.7	6.3
3m	4.9	4.2	8.9	5.4

B.S.=baseline URA=urethra resistant factor WF=Power factor

LEGENDS

Fig. 1 - Microports with radiopacque silicone rubber catheters.

Fig. 2 - AMS 4.5 cm artificial sphincter cuff.

Fig. 3 - Subcutaneously implanted portcatheters to bladder and peritoneal cavity for monitoring urodynamic parameters without urethral manipulation.

Fig. 4 - The x-ray film show subcutaneous portcaths and catheters which were inserted in the bladder and peritoneal cavity.

fig. 5 - A 4.5 cm AMS artificial sphincter cuff was applied loosely around the urethra.

Fig. 6 - The restricting cage.

Fig. 7 - A specially designed sling for keeping the pig comfortably in the erect posture.

Fig. 8 - The minipig model in a restraining cage with a sling.

Fig. 9 - Normal IVP film.

Fig.10 - VCUG show grade I to II reflux on both side.

Fig.11 - A voiding cycle. Numerous artifacts during the collecting phase.

Fig.12 - A collecting phase. Abolition of the artifacts by Ketamine I.M.

fig.13 - A bladder contraction before voiding.

Fig.14 - A tracing showing a normal voiding in minipigs.

Fig.15 - Maximum flow rate is increased with voiding volume and body weight increasing.

Fig.16 - By manual interruption of the flow, isometric detrusor pressure was obtained at zero flow rate.

Fig.17 - A normal pressure/flow plot (low detrusor pressure with high flow rates).

Fig.18 - The pressure/flow plot with a lower normal URA value.

Fig.19 - URA in normal pigs. The horizontal lines from top to bottom represent 100-0 percentiles. The 25th and 75th percentile form top and bottom frame of box. The 50th percentile is within the box.

Fig.20 - Plot of WF against the volume in the bladder. The beginning of voiding is at the right-hand side of the curve, no residual. The curve ends at 0 of volume.

Fig.21 - Comparison of maximum flow(Qmax) in both groups. Qmax is getting lower as a function of time postobstruction in the experimental group.

Fig.22 - 20 weeks after cuff placement, near box-like flow curve with low, fluctuating flow rate and prolonged flow time are shown. The detrusor pressure(Pdet) rise is steep and high.

Fig.23 - The percentage change in the detrusor pressures

preoperative pig, residual-free voiding. The beginning of voiding is at the right-hand side of curve. WF rises to 2.08 W/m^2(A). After 8 weeks obstruction, the voiding with residual urine. WF increased to 11.44 W/m^2. The voiding ceases when the bladder volume is about 150 ml(B).

Fig.35 - Comparison of Piso and WF in normal control and experimentally obstructed group.

Fig.36 - The comparison of Piso and WF before, during and after release of obstruction.

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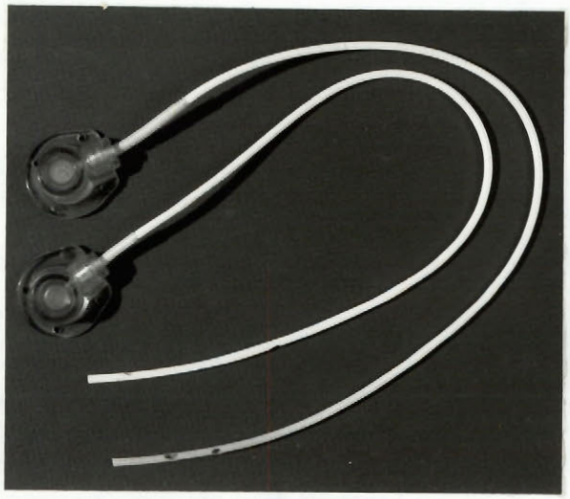
Figure 1



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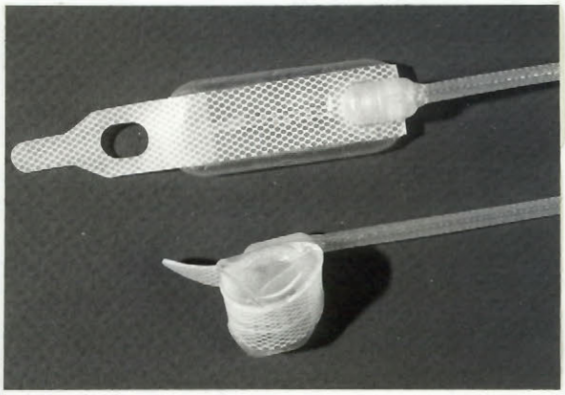

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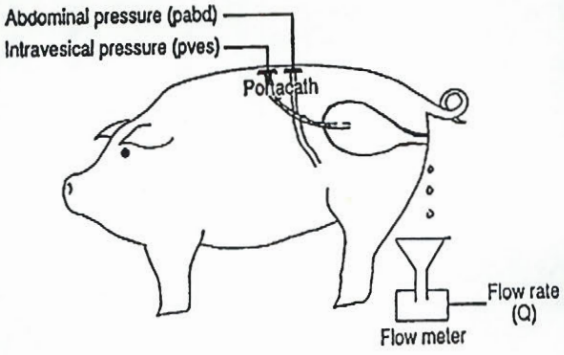

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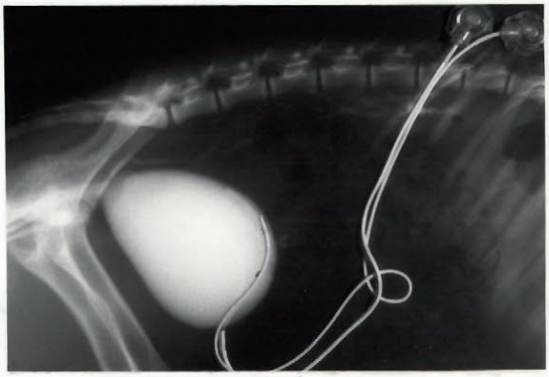

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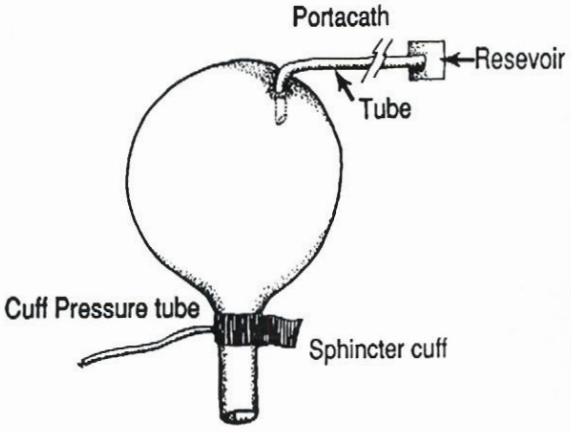

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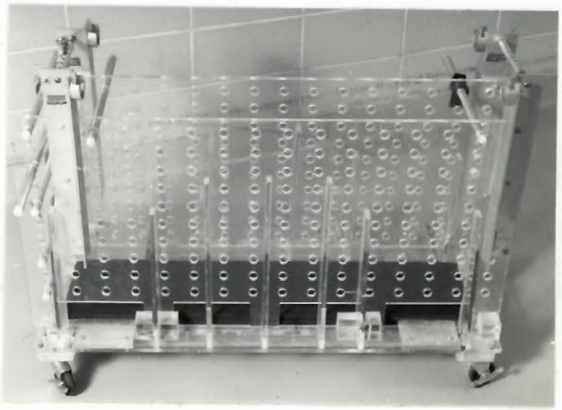

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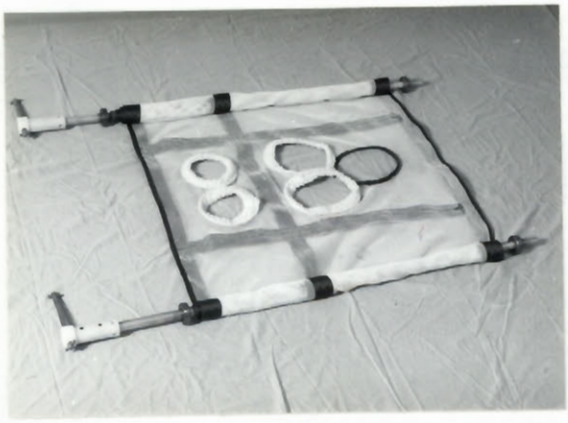

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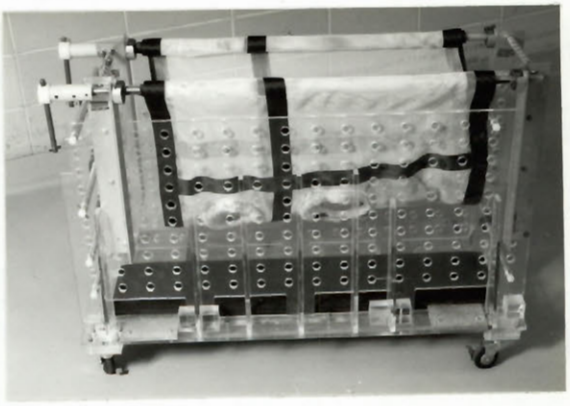

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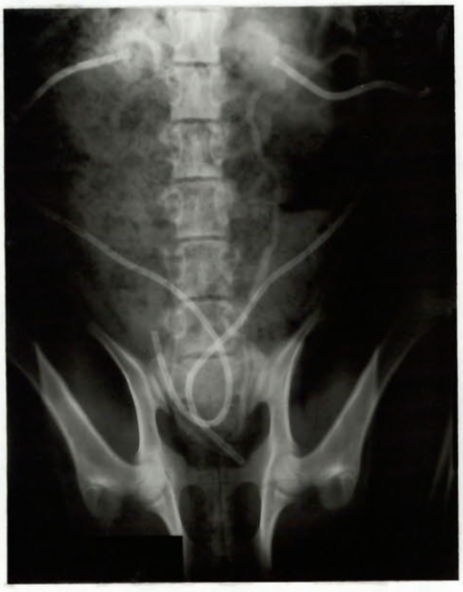

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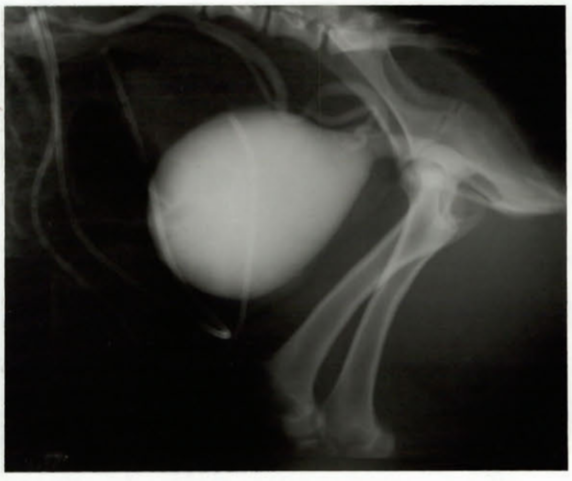

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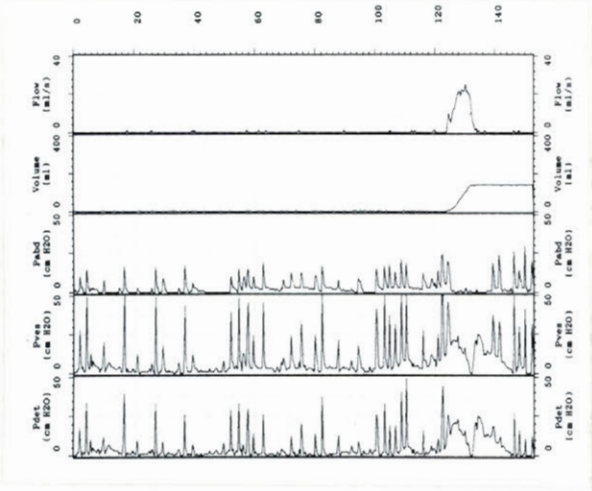

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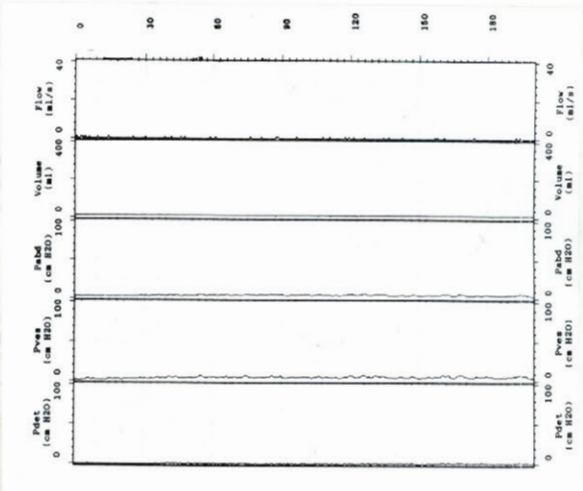

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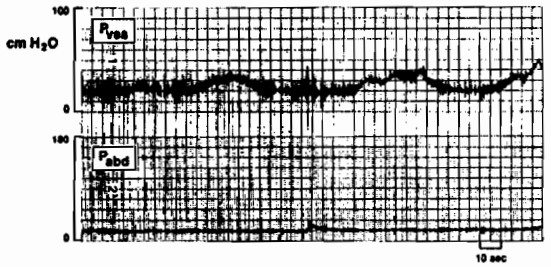

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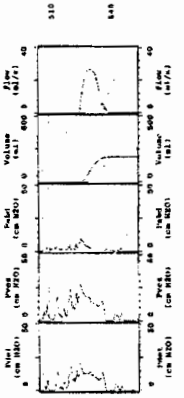
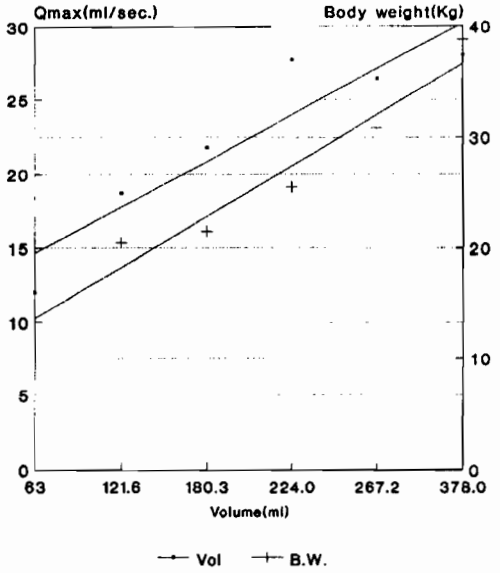


FI915 Qmax-Weight-Vol.Relationship
(Diffrent weight and volume)



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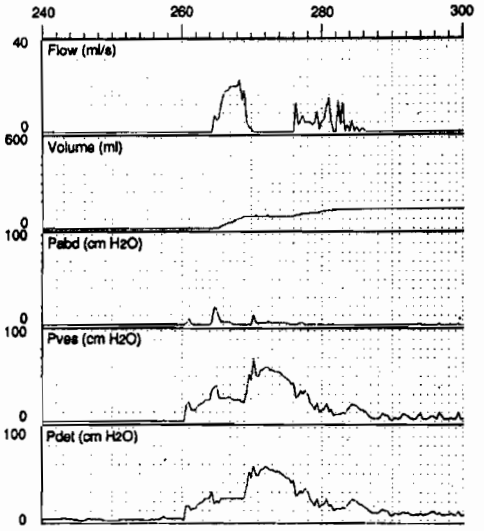

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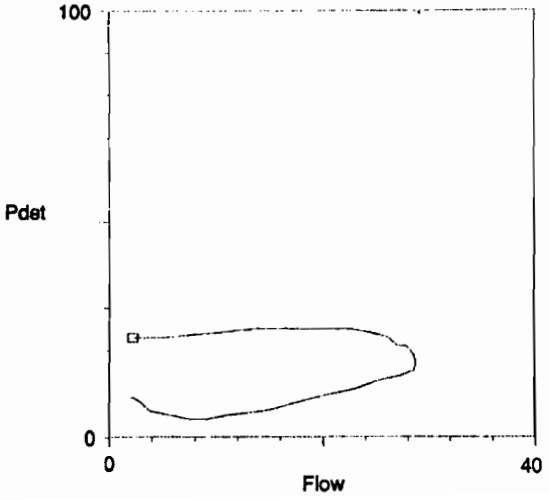

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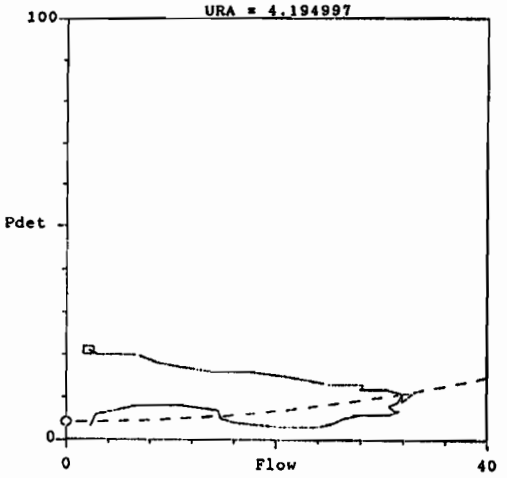
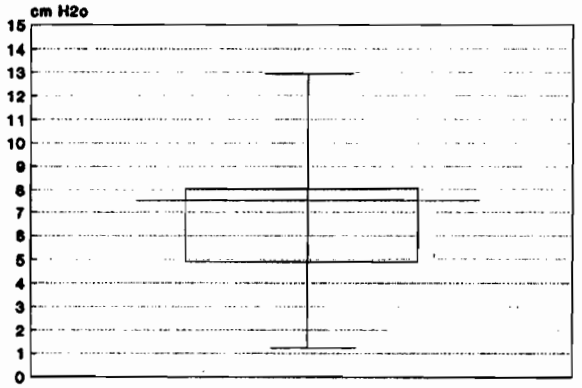


Fig.19 URA Value Distribution



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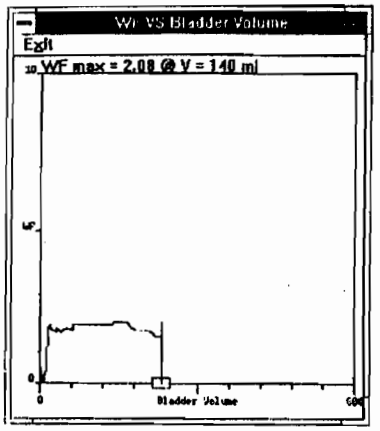
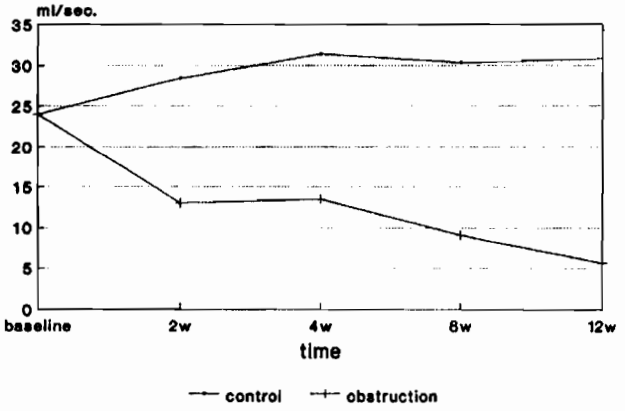


Fig.21 Qmax Change



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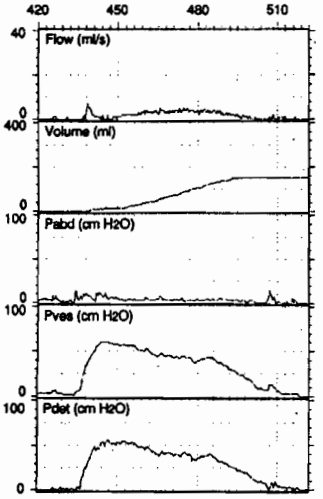


Fig.23 Pressure % Change Postobstruction

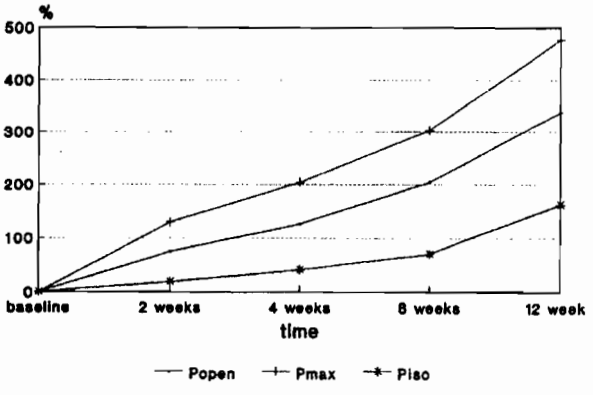


Fig.24 Popen Change

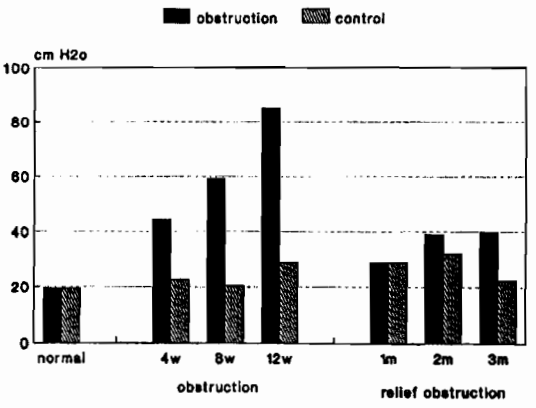


Fig.25 Pmax Change

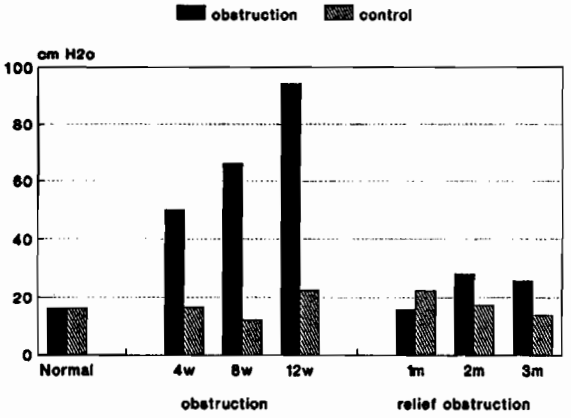


Fig.26 Piso Change

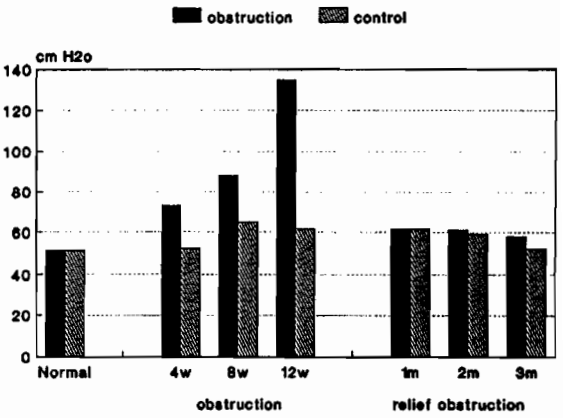
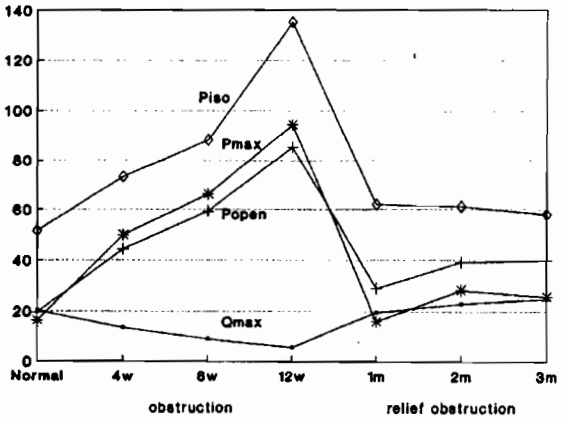


Fig.27 UDS Parameters Change



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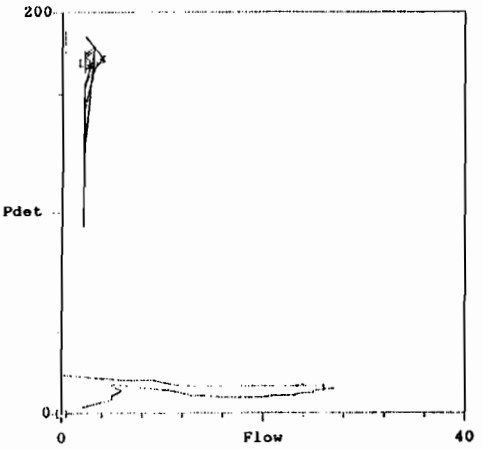

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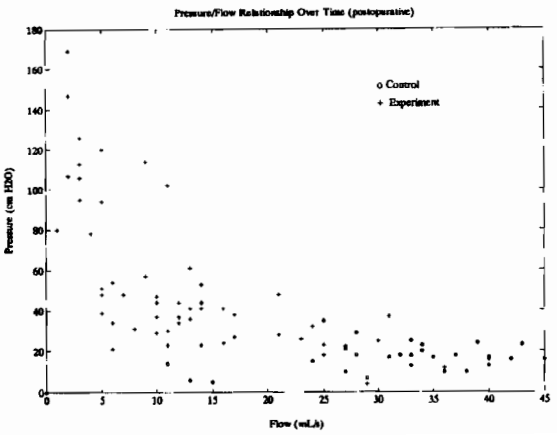


Fig.30 R Value Change
P_{det}/Q_{max}^2

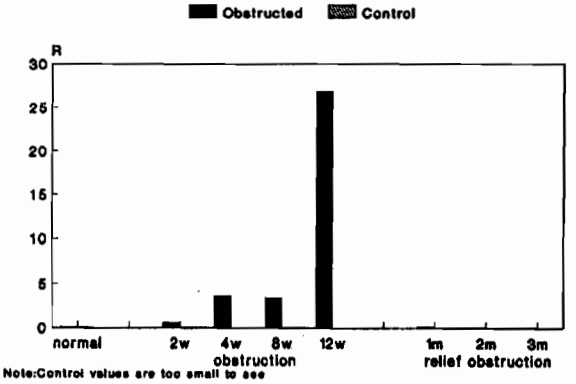


Fig.31 Comparison of PURR

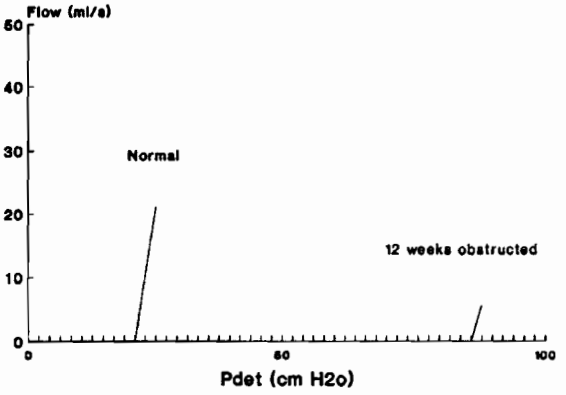


Fig.32 Comparison of Popen and URA

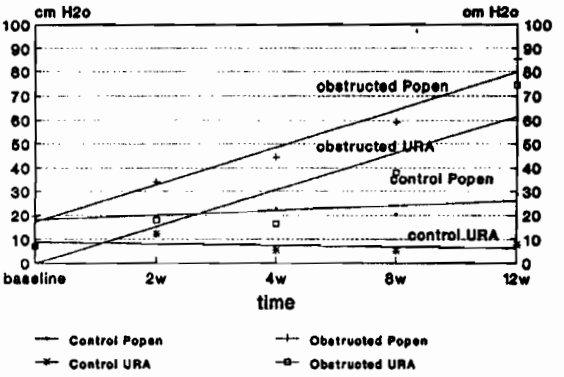
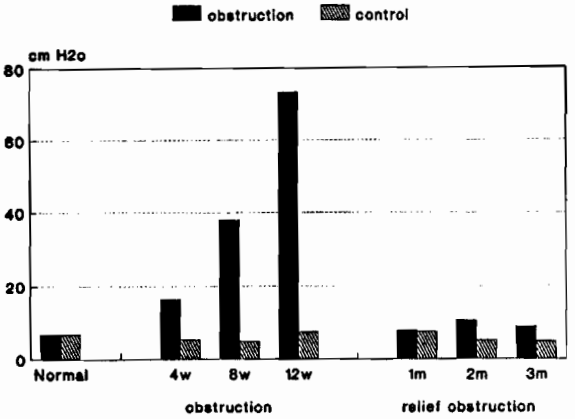


Fig.33 URA Change



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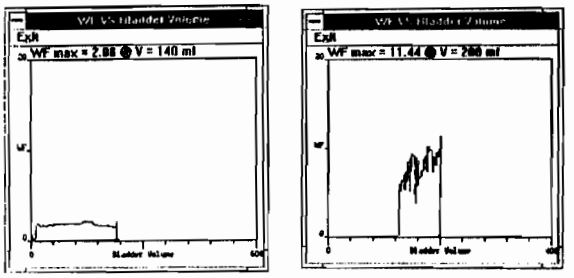

Fig.35 Comparison of Piso and WF

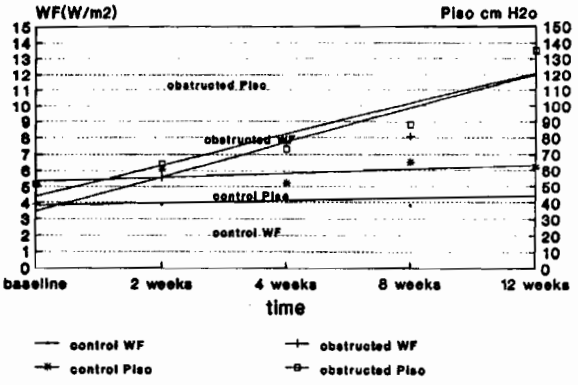

Fig.36 Piso and WF Change