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UNIVERSITY OF CALIFORNIA,
IRVINE

Bladder Diameter Ratio: A Measure Of Bladder Elongation And
Correlation To Bladder Trabeculation in
Children with Spina Bifida

THESIS

Submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

In Biomedical and Translational Science

by

Elias Wehbi MD

Thesis Committee:
Professor Antoine. E Khoury, Chair
Professor Sherrie H. Kaplan
Assistant Adjunct Professor John Billimek

2014

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My number one supporters, my family, whom I love dearly, know how special they are to me. They have taught me the value of hard work, honesty and integrity.

ABSTRACT OF THE THESIS

Bladder Diameter Ratio As A Measure Of Bladder Elongation And Correlation To
Bladder Trabeculation

By

Elias Wehbi,

Master of Science in Biomedical and Translational Science

University of California Irvine, 2013

Professor Antoine Khoury, Chair

To date, there is no widely accepted objective measure to help quantify the shape of the normal urinary bladder in the literature. Patients with spina bifida are a potentially complex population who can present with a spectrum of upper and lower urinary tract derangements. Better understanding of the link between bladder shape in patients with normal bladders and those with spina bifida would greatly add to this understanding. Herein I attempt to shed light on this subject and evaluate a new measure, bladder diameter ratio (BDR), used to quantify the shape of bladders in children with and without evidence of vesicular neurologic pathology.

A small retrospective pilot study evaluated all voiding cystourethrograms (VCUGs) that were performed at our institution in 2010. Those that were performed in children without known bladder pathology or underlying neurologic condition, and read as normal, were included. Patients with spina bifida with and without were

also evaluated. A BDR was calculated in a standard fashion and defined as the ratio of maximal bladder length to width on cystography at cystometric capacity. Mean difference was compared using an independent samples t-test.

Seventy-five children with normal bladders and 63 patients with SB were included with mean ages at time of VCUG of 6.2(0.3-17.6) and 7.2(0.1-21) years respectively, (p=0.2). Children with normal bladders had a BDR of 1.03(95%CI 0.99-1.07). Patients with spina bifida and no trabeculation had no difference in BDR compared to those with normal bladders (BDR=1.04(95%CI 0.96-1.12;p=0.78)), unlike patients with spina bifida and trabeculation (BDR=1.44(95%CI 1.33-1.55;p<0.001).

A larger retrospective study was performed to confirm the findings in a larger cohort of patients with spina bifida and to include ultrasounds, as a possible non-invasive imaging modality to measure BDR and follow patients. A similar analysis was performed which confirmed the similarities with regards to mean BDR between the 3 groups both on both x-ray contrast studies and ultrasound.

There was also a positive correlation between the presence of an elevated BDR and upper tract changes on ultrasound in both studies.

BDR, as a measure of bladder shape in children with normal bladders, can be a useful tool. It provides the first objective measure of normal bladder shape. It can be used as a marker of disease progression. Further studies are needed to correlate BDR with hostile bladder pressures in a prospective fashion.

SECTION I: INTRODUCTION AND BACKGROUND

Introduction and Study Aims

Spina bifida, which literally translates to “split spine”, is one of the most common disorders of the spinal cord contributing to a neurogenic cause of lower urinary tract dysfunction. Due to the nature of the condition and its often-variable presentation, depending on the location and degree of the affected level of the spinal cord, it can present with a spectrum of possible gastrointestinal, orthopedic, neurologic and urologic sequelae. The long term neuro-urologic effects on the urinary tract, especially impact on kidney function, is not completely understood in this potentially vulnerable population. Currently, there are a myriad of tests, some quite invasive, that are performed to both follow and ensure stability of the upper (kidneys and ureters) and lower (bladder and urethra) urinary tracts.

The most commonly used tests to do this, from most invasive to least invasive, are urodynamics, voiding cystourethrography (VCUG) and ultrasonography.

Briefly, urodynamics usually involves pressure catheters in the bladder and rectum to measure several variables associated with filling and emptying of the bladder. It can generate data on pressures in the bladder during filling and voiding to identify those patients at risk for upper and lower urinary tract deterioration should they be exposed to elevated bladder pressures for too long. It can potentially expose children to harmful x-rays if coupled to a video component, which is used to visualize in part, and possibly all of the urinary tract. A VCUG involves a catheter in the bladder and utilizes x-rays and for the sake of this study, can be thought of as

similar to the video component of the urodynamics study. An ultrasound, which is the least invasive of the above-mentioned tests, is an extremely useful and ubiquitous form of medical sonography which utilizes sound waves to generate real-time tomograms of various anatomic structures and only requires an external probe applied against the skin.

Historically, children with spina bifida are followed with regular urodynamics, which again is quite invasive. The standardization of the technique is not ensured at all facilities that offer the procedure and thus, there can be significant variation in the findings of the test. There are also many facilities that do not offer the diagnostic test and so patients who truly require the test may have to travel elsewhere, or wait.(Bauer et al. 2012; Pohl et al. 2002)

An optimal approach to the long term surveillance of these patients with spina bifida is lacking, especially for those patients who have stable and near-normal neuro-anatomy. Many of these patients are quite functional and require little in terms of acute and ongoing care while others require quite the opposite. The issue arises when all patients with this diagnosis, which as can be quite variable, are classified in the same category and managed using the same treatment strategy. A tailored approach would be beneficial as care can be individualized and follow up protocols would vary based on disease severity and markers of progression with regards to the upper and lower urinary tracts. Despite the lack of patient-specific care plans, institutions themselves vary widely in their follow up schemas. There is,

therefore a significant deficiency in robust and high quality evidence to help guide clinicians caring for children with spina bifida.

A new measure that can be incorporated into the existing body of information gleaned from currently used and less invasive tests would be of substantial importance. Such a measure can be correlated with established markers for bladder health, such as low bladder pressures with filling and storage, and with the absence of markers of disease progression, such as bladder trabeculation, without the need for the invasiveness of multiple catheterizations, to help guide care.(Agarwal, Khoury, et al. 1997a; Agarwal, McLorie, et al. 1997b)

There is paucity of literature on objective measures of bladder shape in both children and adults with normal bladders. For this study, individuals with normal bladders can be defined as those individuals who do not have a known neurogenic or non-neurogenic cause of bladder pathology. To create a new measure to better define normal bladder shape would help identify those children at risk for progression, should the bladder shape deviate from this defined normal, possibly even in the absence of overt pathology, such as trabeculation.

The new measure that could be created to help define the normal shape of a urinary bladder, which is not yet a well-defined measure in the literature, is the bladder diameter ratio (BDR), which is explored further in this work.

It will be the aim of this study to help define a set of normal parameters for bladder shape using the BDR. This measure will be both calculated from bladder measurements on both ultrasonography, as well as imaging from both video urodynamics and VCUGs. It is hypothesized that children with otherwise normal bladders will have the same BDRs as those children who have a diagnosis of spina bifida and neurogenic bladder and do not have any evidence of trabeculation on imaging. In contrast, the relationship between BDR in children with spina bifida and trabeculation will also be explored and compared to the other two cohorts of patients, namely those with normal bladders, and those with spina bifida and no trabeculation. This will first be evaluated in a small cohort of patients with spina bifida who underwent video urodynamics. The VCUGs of patients considered to have normal bladders will be used in this initial pilot study as well.

Once the relationship between bladder shape in children with and without spina bifida is better understood, subsequent analysis in a larger retrospective cohort of patients will be carried out to evaluate the role of bladder shape on ultrasound and contrast this to the calculated bladder shape acquired on VCUG and video urodynamics. If it can be shown that a standard ultrasound can add the same information as video urodynamics and VCUGs and avoid the need to perform these invasive tests, costly and resource intensive procedures, patient care will be improved dramatically.

Ultimately, it is the goal of this work to add to the existing body of literature on the role of various imaging modalities used to safely follow patients with spina bifida over time and to tailor care in a patient-specific fashion so as to ultimately reduce the use of invasive testing, such as VCUGs and video urodynamics, in patients who may otherwise be carefully followed with non-invasive tests, such as an ultrasound. To accomplish this, BDR will be evaluated to see if it may be a suitable parameter that can be easily measured, and when similar to a calculated normal value derived from patients without neurogenic bladder pathology, may reassure the clinician that further invasive testing could be spared.

Background

Characteristics of Urethral Sphincteric Function and the Normal Bladder

The main components of the lower urinary tract are the bladder, urethra and the sphincteric muscles responsible for continence, of which there are both internal and external structures. The internal sphincter is an area represented by the region of the bladder neck and the proximal urethra.(Agarwal & Bagli 1997) The internal sphincter is not a discrete structure but can be thought of as a physiologic mechanism that helps maintain urinary continence of the bladder neck and proximal urethra.(Agarwal & Bagli 1997) This has been confirmed on radiographic studies and on measurements of urethral pressure profiles.(Yucel & Baskin 2004) The external sphincter is derived from skeletal muscle from the inner fibers of the levator ani muscles and surrounds the urethra as it traverses the deep perineal pouch(Shah et al. 2014) In males it covers the inferior side of the prostate and is

located at the level of the membranous urethra.(Jung et al. 2012) In females it begins at the inferior end of the bladder and includes several structures including the compressor urethrae muscles and the urethrovaginal sphincter.(Macura et al. 2001; Macura & Genadry 2008; Jung et al. 2012) Several studies evaluating the complexity of continence have shown the elaborate association between sphincteric control in both males and females and their intricate relationship to the numerous surrounding structures of the pelvic floor muscles and tendinous attachments, all of which works in unison to attain continence of the urinary bladder, even when intravesical pressures increase dramatically.(Shah et al. 2014; Wallner et al. 2009; Sebe, Schwentner, et al. 2005b; Sebe, Fritsch, et al. 2005a)

The urinary bladder is a structure, that when is empty, lies within the true pelvis. It acts as a reservoir that was designed to hold a significant amount of urine with little changes in overall pressure. As it fills, the bladder rises anterosuperiorly into the abdomen towards the umbilicus. When empty, it takes on a tetrahedral shape, but when full, it is more spherical,(Shah et al. 2014) Histologically, the bladder is made of multiple layers, including a mucosal layer, muscularis propria and the adventia and is devoid of trabeculation, which is a sign of muscle hypertrophy.(Agarwal & Bagli 1997; Shah et al. 2014).

There are essentially 2 phases to the elimination of urine from the urinary bladder after it is transported down from the renal units; the storage phase – where the bladder acts as a reservoir to collect urine, and the voiding phase – which can be

initiated on command when voiding is desired and a minimal volume of urine present, or when a threshold volume is reached.(Shah et al. 2014) Storage of urine and micturition are controlled by a complex network of nerves from both the central and peripheral nervous systems. Figure 1 illustrates these connections and is encapsulated nicely in the accompanying text by Fowler et al.(Fowler et al. 2008)

Figure 1: Neural circuits that control continence and micturition.

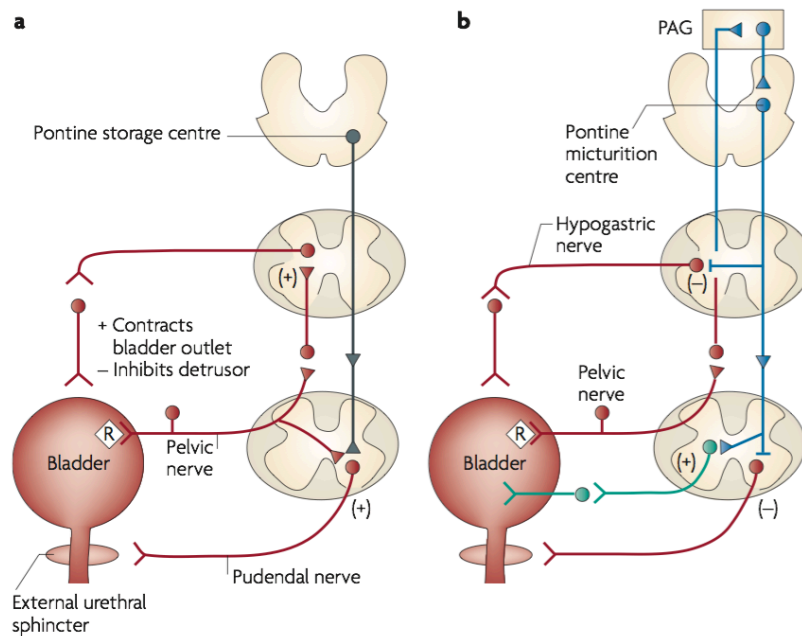


Figure 1-a

“...shows the urine storage reflexes. During the storage of urine, distention of the bladder produces low-level vesical afferent firing. This in turn stimulates the sympathetic outflow in the hypogastric nerve to the bladder outlet (the bladder base and the urethra) and the pudendal outflow to the external urethral sphincter. These responses occur by spinal reflex pathways and represent guarding reflexes, which promote continence. Sympathetic firing also inhibits contraction of the detrusor muscle and modulates neurotransmission in bladder ganglia. A region in

the rostral pons (the pontine storage centre) might increase striated urethral sphincter activity." {Fowler:2008dc}

Panel b of Figure 1 discusses voiding reflexes,

"...During the elimination of urine, intense bladder-afferent firing in the pelvic nerve activates spinobulbospinal reflex pathways (shown in blue) that pass through the pontine micturition centre. This stimulates the parasympathetic outflow to the bladder and to the urethral smooth muscle (shown in green) and inhibits the sympathetic and pudendal outflow to the urethral outlet (shown in red). Ascending afferent input from the spinal cord might pass through relayneurons in the periaqueductal grey (PAG) before reaching the pontine micturition centre. Note that these diagrams do not address the generation of conscious bladder sensations, nor the mechanisms that underlie the switch from storage to voiding, both of which presumably involve cerebral circuits above the PAG. R represents receptors on afferent nerve terminals." {Fowler:2008dc}

In summary, in order to achieve safe continence, the complex network of nerves and structures needed to work in unison to ensure that the bladder is able to hold a capacity of urine for a socially acceptable period of time and do so with minimal changes in pressure.

Spina Bifida

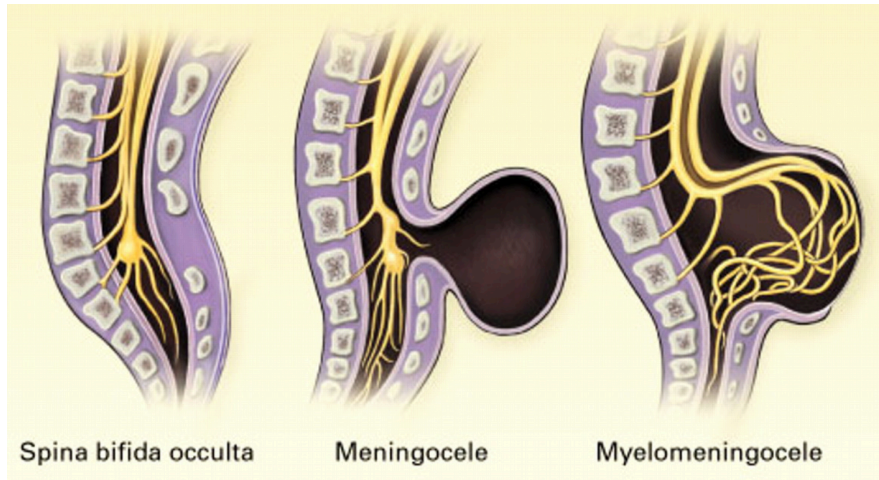
Spina Bifida is a condition which affects approximately 1:1000 live births worldwide with several racial and geographical variations.(C S Chung 1968) In the United States it affects approximately 0.7:1000 live births with a greater predilection to

affecting whites and a tendency to have a higher incidence on the East Coast of the country.(Lemire 1988) Hispanic infants consistently have the highest incidence of spina bifida compared to other ethnic groups.(Boulet et al. 2008)

There has been a significant reduction in the rates of SB with pre-natal supplementation and fortification of the food supply with folic acid, which has led to a reduction in the presence of neural tube defects, such as spina bifida.(Boulet et al. 2008)

Myelodysplasia is an all-inclusive term used to describe the various abnormal conditions of the vertebral column that affect spinal cord function.(Wein & Louis R Kavoussi 2012) There are three main categories commonly used to describe the specific types of myelodysplasia, which are illustrated in Figure 2. These are meningocele, which involves herniation of the meninges of the spinal cord but does not contain any neural elements extending beyond the limits of the vertebral canal, myelomeningocele, where neural tissue, either nerve roots or portions of the spinal cord have evaginated with the meningocele, and lastly, lipomyelomeningocele, where fatty tissue has developed with the cord and both protrude with the sac beyond the vertebral canal.

Figure 2: Illustration describing common categories of myelodysplasia.
Illustration was taken from
<http://www.humpath.com/spip.php?article1225>



Myelomeningocele is by far the most common form of myelodysplasia and accounts for more than 90% of all open spinal dysraphic states.(Shurtleff 1980; Artibani et al. 1990; Wu et al. 1997) Figure 3 shows a patient with an open myelomeningocele.

Figure 3: Typical appearance of an open myelomeningocele in a neonate.



Figures 4 and 5, taken from Guggisberg et al, highlight the variable presentation of the disease which can manifest in both occult or cutaneous spinal lesions.(Guggisberg et al. 2004)

Figure 4: Clinical features of occult spinal dysraphism. a) Sacral lipoma and deviated gluteal furrow, b) lumbar port-wine stain, lipoma, dermal sinus, and deviated gluteal furrow, c) dorsal and lumbar unclassified hamartomas. (Guggisberg et al. 2004)

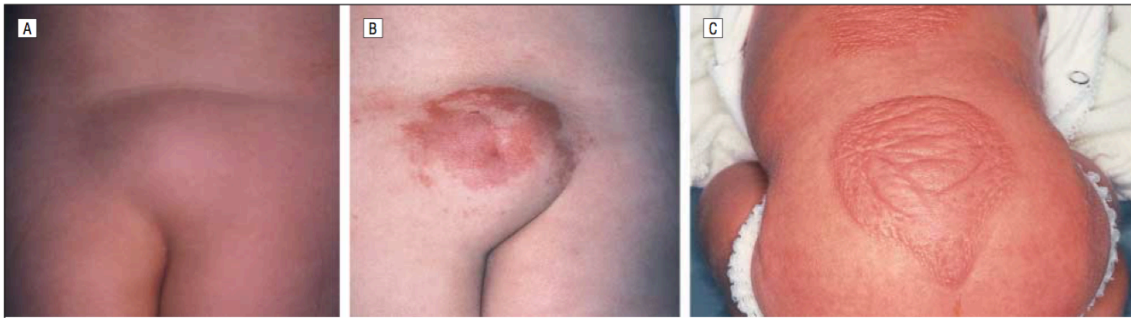
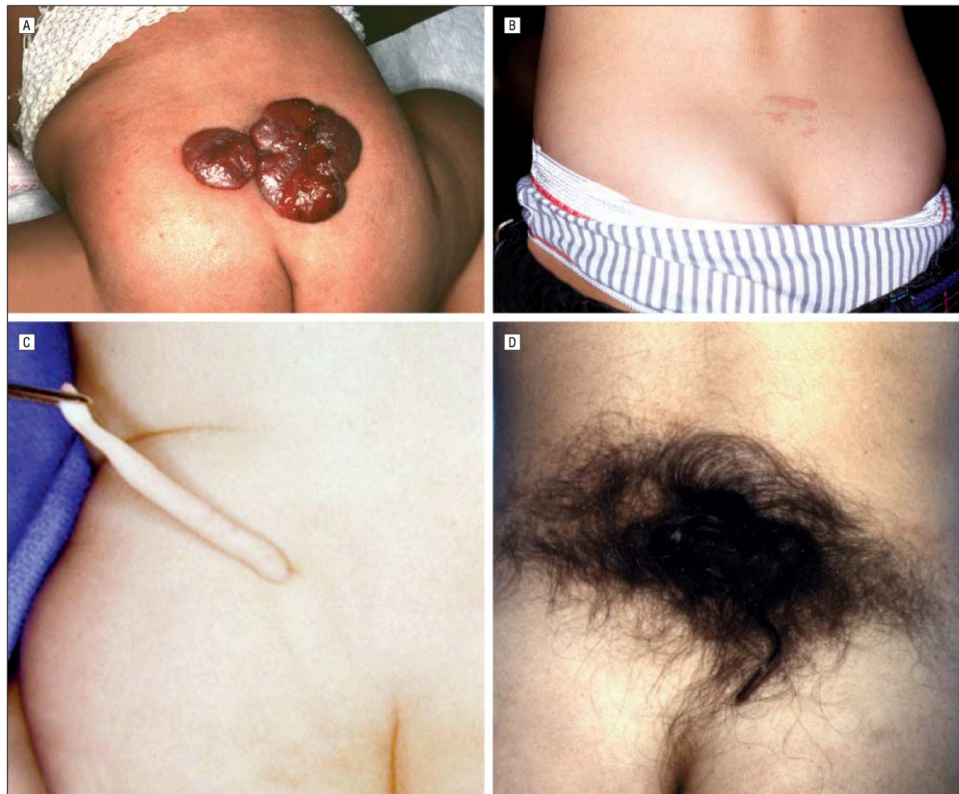


Figure 5: Clinical aspects of isolated or combined congenital lumbosacral cutaneous lesions. a) Ulcerated hemangioma centered on a dermal sinus and deviation of the gluteal furrow, b) isolated port-wine stain, c) human tail d) faun tail. (Guggisberg et al. 2004)



Although spinal defects can occur at any level, most occur at the level of the lumbar and lumbosacral vertebrae, with a lower incidence for involvement of the sacral, thoracic and cervical areas, in order from most to least common.(Bauer et al. 1977)

And although the level of the neurologic lesion can be quite variable, often it depends on the contents of the neural elements that have herniated into the meningocele sac that impact the type and severity of lesions produced, and not the

vertebral level, which can occasionally predict very little. (Wein & Louis R Kavoussi 2012)

Definitive treatment for children with open spinal dysraphic conditions is early surgery, usually shortly after birth and ensuring a sterile environment for the open lesion. Many of these children require multidisciplinary medical treatment to manage several aspects of their care, which may include neurosurgical, orthopedic, gastrointestinal, neurologic and urologic specialties, to name a few. There is usually also a complement of allied health services to manage both psychosocial and functional aspects of the child's care.

Although historically surgery to close the spinal defect occurs shortly after birth, there has been a shift to in utero surgery to close the defect prior to birth, usually around 25 weeks gestation.(Tulipan & Bruner 1998; Shapiro 2000) And while the long term data is not definitive, there appears to be a reduction in the rates of shunt dependent hydrocephalus, a source of potential complication and frequent neurosurgical intervention.(Holzbeierlein et al. 2000; Tulipan et al. 2003)

Ultimately, children with this condition present with a spectrum of severity and it is often difficult to predict from the initial assessment and thus close follow up is required for the variety of multi-system involvement. A novel tailored approach directed at the child's unique condition would be invaluable and added information

that may be able to predict progression of the disease or decompensation of the upper or lower urinary tracts would be helpful to both clinicians and patients.

The Neurogenic Bladder

The most common cause of neurogenic bladders in children is spinal dysraphism.(Holzbeierlein et al. 2000) The term neurogenic bladder is a general one that refers to the dysfunction of the urinary bladder due to the disease of the central nervous system or peripheral nerves involved in with storage or micturition. It may have a variety of clinical manifestations such as incontinence, retention and may even be present in a child who may seemingly void without significant difficulty, but aspects of the voiding could have detrimental consequences to renal function if they persist. Some of these issues are usually associated with elevated intravesical pressures and potential reflux.(Sager et al. 2013; Agarwal, Khoury, et al. 1997a; Agarwal, McLorie, et al. 1997b)

Due to the various degrees of affectedness and severity of lesions, patients with seemingly similar pathology can present with quite different functional outcomes. The close follow up of children who may progress to lower urinary tract deterioration after a diagnosis of spina bifida is critical, as progression of the underlying bladder dysfunction can result in significant deterioration of the lower urinary tract, illness due to infections, difficulties with voiding and ultimately damage to the kidneys. If left untreated, bladders may decompensate, giving rise to the characteristic trabeculation and elongation of the bladder that is seen in some patients with spina bifida, shown here in Figure 6. Close

follow up of patients has shown a significant improvement in several aspects of their care.(Dik et al. 2006)

Figure 6: Image from study patient demonstrating characteristic elongated bladder and bladder wall irregularity characteristic of trabeculation.

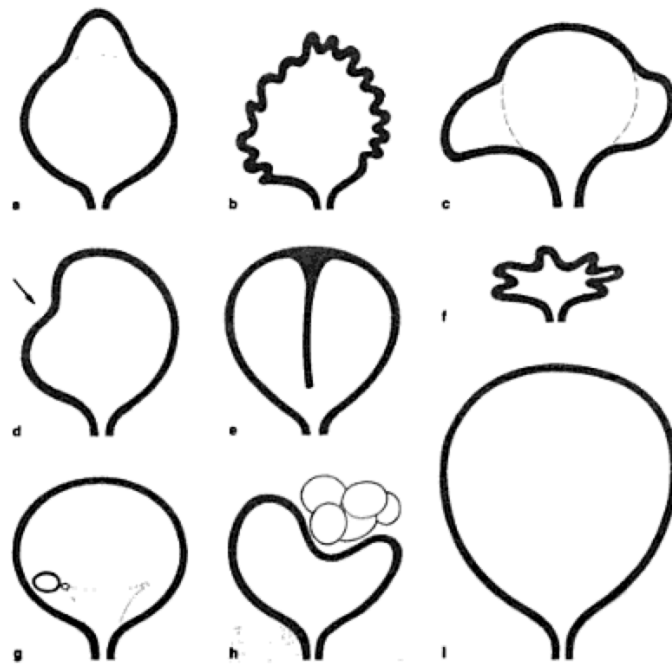


Bladder Shape and Trabeculation on Imaging

There has been considerable debate as to what constitutes a normal bladder across multiple imaging modalities and investigative procedures. Several studies have attempted to provide insight into describing the characteristics of what constitutes a normal bladder. Some have looked at intravesical pressures, others have looked at bladder shape.(Austin et al. 2014; Agarwal & Bagli 1997; Ebel & Benz-Bohm 1999; Esposito et al. 2006) In reality, there is very little data on objective measures to describe normal bladder shape, and thus be able to identify what is quantitatively

abnormal. An illustration shown in Figure 7, taken from Ebel's book illustrates some of the possible shapes that have been described in literature, although oftentimes much of these descriptions are based on little objective evidence and may be of little value clinically.

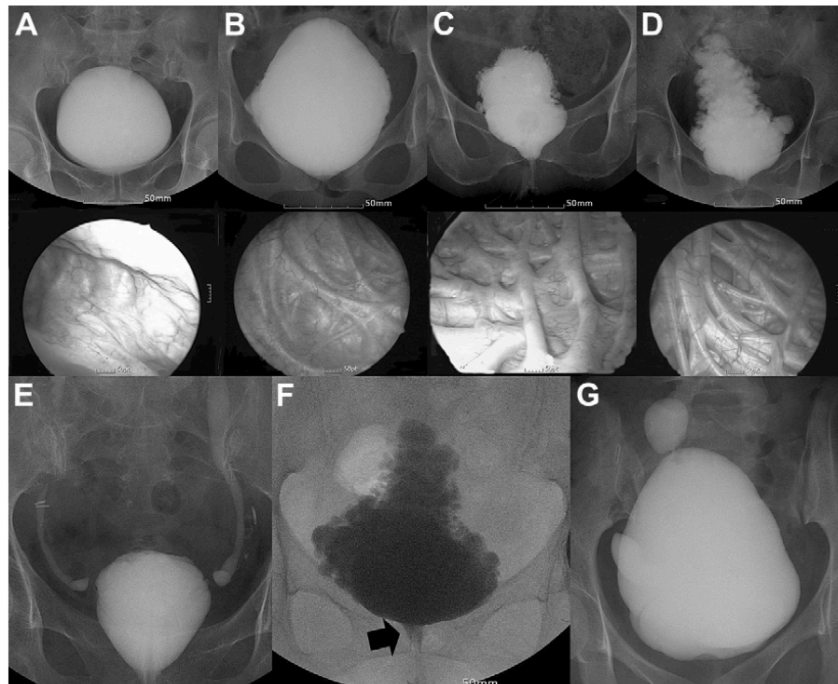
Figure 7: Variations in bladder shape and position. a) Urachal diverticulum b) Christmas tree shape, c) Bladder ears, d) Postoperative bladder e) Septate bladder, f) Shrunken bladder, g) Paraureteral diverticulum, h) Extrinsic compression i) Lazy bladder



Trabeculation is definitively diagnosed on cystoscopic evaluation and denoted by hypertrophy of bladder detrusor muscle that results in intravesicular contour changes with or without cellules, saccules or diverticulae.(Cho et al. 2013) Several suggestions for grading systems have been provided but there is not yet any widely accepted method to grade bladder trabeculation(Cho et al. 2013; Khoury et al.

2008). An example of this is described in the work by Cho and colleagues which uses findings from contrast studies to suggest a novel grading system for bladder trabeculation, and is illustrated in Figure 8.(Cho et al. 2013)

Figure 8: Proposed grading system for bladder trabeculation. a) Grade 0 (no trabeculation), b) grade 1 (mild trabeculation with <5 mm of maximal depth and <1/2 area of bladder), c) grade 2 (moderate trabeculation with >5 mm and <10 mm and >1/2 area of bladder), d) grade 3 (severe trabeculation with >10 mm and >1/2 area of bladder), e) vesicoureteral reflux, f) urethral leak, and g) bladder diverticulum.



To date, there are still no widely accepted objective and quantitative measures of normal bladder shape. Considering that bladder measurements may be impacted by age, size, gender, to name a few, a ratio of bladder height divided by the bladder

width on a standard image, such as a VCUG or ultrasound, may be better suited to help define normal bladder shape. Calculating the new measure by using a standard image may help overcome variations in image acquisition between the different imaging modalities. Conversely, the use of a ratio may negate the need for standard image acquisition as the calculated ratio may approach a constant value once a threshold volume is achieved during bladder filling. The merits of both these approaches will be discussed further in this study.

SECTION 2: METHODS

Method for Creation of Measurement

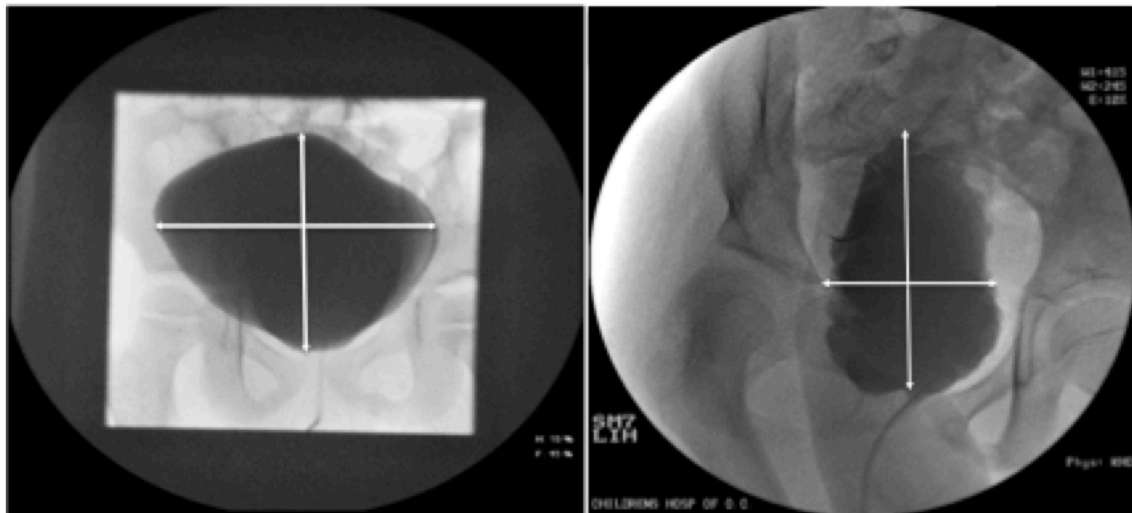
Keeping in mind possible frameworks, the proposed model here would fit within the conceptual framework of a reflective model as all measures reflect the same underlying construct, defining what constitutes a “normal” bladder. Since there is no established normal value for bladder shape, for this measurement framework, the accepted gold standard must be those images captured on both VCUG or video urodynamics. The process then requires defining a new measure that is related to that gold standard, the new measure ultimately being BDR on ultrasound and then validating this new measure with the use of a more accepted imaging modality, VCUG and video urodynamics.

BDR was used to help define the normal shape of the urinary bladder and has which has not yet been well-described in literature. As noted, several authors have defined the theoretical shape of the normal urinary bladder, but to date, there are no apparent well-defined, objective parameters to quantify normal bladder shape in humans.

Defining the parameters of a new, “normal” measure for a previously undefined parameter, such as BDR, requires the creation of a new and acceptable “normal value”. The proposed new measure, BDR, is the ratio of the midpoint of the bladder height to the midpoint of the bladder width on the antero-posterior view on a VCUG at maximum cystometric capacity. To calculate BDR on video urodynamics, the BDR

represents the midpoint of the bladder height over the midpoint of the bladder width on the video component of urodynamics using the same antero-posterior view and this will also be calculated at the maximal cystometric capacity. Should there be a leak observed at the time of the urodynamics, which can be seen during the procedure, the BDR will be calculated using the image acquired just prior to the identified “leak” event. See Figure 9 for example of BDR calculation.

Figure 9: Calculation of bladder diameter ratio on x-ray contrast studies. Calculation is taken from the antero-posterior image at maximal cystometric capacity.



$$\text{BDR} = \frac{\text{Bladder Height}}{\text{Bladder Width}}$$

The maximal cystometric capacity is the maximal volume that the bladder can hold immediately prior to voiding. Using the maximal cystometric capacity will help

adjust for the inherent variability of the bladder shape as it fills. Secondly, the maximal cystometric capacity is generally an image that is acquired on both VCUGs and on video urodynamics across all institutions.

It is well known that the shape of the bladder changes in the presence of trabeculation and certain neurogenic conditions, shifting to an increasing height and giving the bladder a “longer” appearance on imaging, even though there are no defined objective measures of this feature.(Borzyskowski & Neville 1981) In a bladder with significant trabeculation and high bladder pressures, the BDR might be expected to increase, whereas in normal bladders, the BDR is expected to be closer to 1, as the shape of the bladder on the imaging at maximal cystometric capacity tends to approach the shape of a sphere, although there is little robust quantitative evidence in the literature to support this claim.

Again, “normal” needs to be defined in a group of patients without any spinal anomalies, such as SB, and without the presence of a neurogenic bladder and should be expected to have normal bladder pressures on VUDS. Although no urodynamics were performed on patients with normal bladders in this study, due to the invasiveness of the procedure, it would be highly unlikely that children included into the group used to define “normal” BDR, especially with a normal VCUG, would have elevated bladder pressures on urodynamics. The absence of any signs or symptoms on medical history and physical exam, which are both elicited at time of clinic visit, especially on a detailed health questionnaire, which is completed by all

patients seen in the clinic from where the patients with normal bladders were drawn, would make it unlikely that there would be children with neurogenic bladders included in the “normal” cohort. Also, those VCUGs with findings suggestive of neurogenic bladder pathology, such as the presence of trabeculation, were excluded. It would also be unjustifiable to carry out urodynamics in this patient population as no clinical indications exist and the procedure is overly invasive.

The renal ultrasounds on all patients with normal bladders were reviewed to look for any upper tract pathology such as hydronephrosis. The presence of vesicoureteral reflux was also identified on both VCUGs and video urodynamics. Any clinically significant abnormalities were identified and recorded. Having a normal VCUG was one of the inclusion criteria for entry into the group of patients with normal bladders used to define a normal value for BDR. A normal VCUG was defined as a VCUG with an antero-posterior image at maximal cystometric capacity without the presence of vesicoureteral reflux, a diverticulum, trabeculation or bladder neck pathology.

Since there is no established normal value for BDR, one needs to be defined. In the first portion of this study, a small cohort of patients who did not have a diagnosis of neurogenic bladder, had no history of bladder surgery, who had a normal VCUG, and who had one for reasons other than to evaluate the presence of a neurogenic bladder, such as after a urinary tract infection, had their VCUG images evaluated and

the BDR was calculated. These patients were captured. Patients also had to have had an ultrasound of the upper and lower urinary tracts within 2 weeks of the VCUG. Patients were excluded from the “normal” if they failed to meet inclusion criteria, or did not have images available for viewing, such as in those patients who came to the clinic with only reports from one or both tests.

Parameters such as age and bladder volume were considered in an attempt to detect an effect on BDR. BDR was adjusted for both age and bladder volume separately. The BDR calculated from this group was compared to the BDR calculated from a group of patients who have a known diagnosis of spina bifida to see if there was a difference. One of the hypotheses is that an elevated BDR may be a negative prognostic indicator and may in fact be associated with the presence of trabeculation. To examine this relationship, patients with SB were stratified into two groups, those patients with trabeculation and those without trabeculation. The mean BDRs of these groups were compared with T-test to compare mean BDRs of these groups looking for a statistically significant difference, with a p value of less 0.05 using SPSS software version 21.

Once the relationship between BDR of patients with normal bladders and those with a suspected diagnosis of neurogenic bladder was understood, a larger sample of patients with normal bladders was collected, with their corresponding ultrasounds and compared to a larger cohort of patients with SB who underwent video

urodynamics. Corresponding ultrasounds were also evaluated and as above, mean BDRs were compared once stratified for trabeculation.

In the larger cohorts, in an attempt to correlate the BDR calculated from a standard ultrasound in patients with normal bladders and those with SB, the analogous measurements for BDR were calculated from the ultrasounds in both groups. The measurement corresponding to the bladder height on a VCUG was the measurement on the horizontal axis on the standard “long” view of the bladder and the measurement corresponding to the bladder width on a VCUG was the measurement of the horizontal axis on the standard “trans” view of the bladder on the ultrasound. The same steps were repeated for patients with SB. Attempts were made to identify trabeculation on the both VCUGs and video urodynamics, as well as ultrasounds. Mean BDRs between all groups were compared using a T-test looking for statistical significance with p value less than 0.05 using SPSS software version 21.

A unique issue with ultrasounds is the dramatic variation in volumes seen at the time of ultrasound. This may or may not affect the relationship between BDR across imaging modalities because, as defined earlier, BDR on VCUG and video urodynamics is measured at maximal cystometric capacity. This is not always the case during image acquisition on ultrasound.

Not only was BDR calculated and compared between the 3 cohorts for either ultrasound and VCUGs or video urodynamics studies, since BDR is a ratio, attempts were made to look at the BDR across imaging modalities for the same patients, namely VCUG and ultrasound for normal patients. BDR will be evaluated for the entire cohort, in this fashion, but also, an attempt was made to include only ultrasounds that had an expected volume within 20% of the expected volume for theoretical bladder capacity using the formula by Koff described below:

$$\text{Bladder volume (in ounces)} = \text{Age} + 2$$

to better mirror the image that would be acquired on a VCUG and video urodynamics for BDR calculation. (Koff 1983) Several other formulas to estimate expected bladder capacity have been put forth, but the above mentioned formula is still one of the most widely used in literature to date. (Martínez-García et al. 2014)

Tests for significance were made with a Fisher's Exact Test (SPSS Version 21) between the presence of upper and lower urinary tract pathology, namely hydronephrosis and reflux, with BDR and the presence of trabeculation. Significance was defined as having a p value less than 0.05.

VCUG and Ultrasound to Describe Trabeculation

While assessing the meaningfulness of BDR in describing the shape of the bladder in patients with no underlying vesicular neurogenic pathology and those with spina

bifida, who would certainly be at risk for such a diagnosis, trabeculation was used as a key dichotomizing variable for the evaluation of BDR. Its presence is an accepted prognostic indicator of bladder deterioration. The ability to detect trabeculation has been historically mostly accomplished by the use of x-ray contrast studies, such as VCUGs and video urodynamics. For this study, attempts were made to evaluate the ability of an expert viewer to identify trabeculation on an ultrasound.

Identifying trabeculation on ultrasound is an important step as this work intends to assess whether BDR and the absence of trabeculation on ultrasound can be used to identify patients who can be safely monitored without the need for further invasive studies. Correlations between the two imaging modalities were assessed using a two-tailed Pearson Correlation with significance defined as a p value of less than 0.01. Agreement between the ability to identify trabeculation on both imaging modalities was evaluated using Cohen's Kappa coefficient for inter-annotator agreement. Both statistical models were conducted using SPSS Version 21.

Validity

Face validity is a prerequisite in the development and testing of a new measure and will be achieved with the use of a clinical expert. Based on the relationship between BDR on video urodynamics and BDR on ultrasound as measures of the same construct, face validity appears to be achieved as the test sets out to measure the bladder shape, represented by the BDR and it does appear to do so.

Content validity is also an important to establish the psychometric properties of the new measure. Several studies have attempted to describe bladder shape in a 3-dimensional form, but none have yet described an objective measure in humans. BDR does not represent all the facets of bladder shape, which would improve the degree of content validity, but it does serve an important dimension of this criterion.

Criterion validity describes the extent to which a variable is associated with an established measure of the same construct, or gold standard. Associations between BDR on VCUG and video urodynamics were compared to that obtained on ultrasound to correlate abnormal upper tract findings on an ultrasound. A high degree of criterion validity and predictive validity would support the use of BDR on ultrasound to be used as a indicator of stability over time. Should there be a range of BDR linked to abnormal changes seen on renal imaging or on VCUG, BDR may be able to predict the abnormal findings and may suggest the need for closer surveillance in some patients.

Domain of Observables

In order to generate parameters need to calculate BDR on VCUG, video urodynamics and ultrasound, a data dictionary was created with several variables captured from the above-mentioned imaging, along with basic demographic data. The complete list of features constitute the domain of observables, as listed below:

- Bladder height on antero-posterior view on VCUG
- Bladder width on antero-posterior view on VCUG
- Bladder height on antero-posterior view on video urodynamics
- Bladder width on antero-posterior view on video urodynamics
- Bladder height on ultrasound (horizontal axis on standard long view)
- Bladder width on ultrasound(horizontal axis on standard trans view)
- Bladder volume on urodynamics*
- Bladder volume on ultrasound
- Theoretical bladder volume (Formula)
- Maximum hydronephrosis grade on ultrasound
- Maximum ureteral diameter on ultrasound
- Ultrasound bladder thickness
- Ultrasound rectal diameter
- Presence of trabeculation on VCUG
- Presence of trabeculation on video urodynamics
- Presence of trabeculation on ultrasound
- Maximum vesicoureteral grade on VCUG
- Maximum vesicoureteral grade on video urodynamics
- Volume at which vesicoureteral occurs on VCUG
- Volume at which vesicoureteral occurs on video urodynamics
- Urodynamic maximum cystometric pressure
- Anticholinergic usage
- Botox injection or previous surgery

- Alpha blocker usage

* Note that bladder volumes on VCUGs are not consistently reported

The above list will be used to help calculate confounders (e.g. age at time of study) or may be confounders themselves (e.g. presence of anticholinergic usage, or presence of constipation – measured by rectal diameter).

To validate BDR, several experienced individuals were used to calculate BDR and then randomly verified by an expert clinician.

SECTION 3: RESULTS

A. Initial Pilot Study

Children with normal bladders

All VCUG's performed at our institution in 2010 for reasons other than a diagnosis of SB or neurogenic bladder were evaluated. Of the 95 VCUGs reviewed, 75 had corresponding ultrasounds performed within 2 weeks of the study. Mean age of this group was 6.2 years. The mean BDR of this group was 1.03 (SD 0.18, 95%CI 0.99-1.07).

Children with SB

During the same time period, all video urodynamics of children with SB who had a corresponding ultrasound within 2 weeks of the urodynamics were evaluated. In all, 63 patients were included in this group. The mean BDR of this group was 1.26 (SD 0.36, 95% CI 1.17-1.35)

When children with SB were stratified for the presence and absence of trabeculation as observed by a trained evaluator on a VCUG, there were 28 patients without trabeculation on video urodynamics imaging and 35 patients with trabeculation. The mean BDRs for these groups were 1.04 (SD 0.21, 95% CI 0.96-1.12) and 1.44 (SD 0.35, 95% CI 1.33-1.55) respectively.

Intergroup comparisons

Comparison of mean BDRs of the children defined to have non-neurogenic bladders with those with SB and no trabeculation showed a less than 1% difference with a non-statistically significant p value of 0.78. Comparison of mean BDRs for those children with SB without trabeculation to those with SB and trabeculation yielded an almost 40% difference between the groups with a highly statistically significant difference, $p < 0.001$. All calculations were carried out using a two-tailed Student's t-test.

Comparison of the presence of upper tract changes, namely the presence of any vesicoureteral reflux or any hydronephrosis revealed a statistically significant difference between those children with SB and no trabeculation and those with SB and trabeculation with event rates of 4 and 13 respectively, (14.2% vs 37%, $p < 0.05$) using a Fisher's Exact test.

The above mentioned data is summarized in Table 1.

Table 1: Summary of means for BDRs and upper tract findings for patients with normal bladders, and those with spina bifida with and without trabeculation.

| | Patients (n) | Ages (yrs) | BDR | 95% CI | % Change | p Value | Upper Tract Changes n (%) | p Value |
|--------------|-------------------------|-----------------------|------------|---------------|---------------------|-------------------|--|----------------|
| NRMB | 75 | 6.2 | 1.03 | 0.99-1.07 | | | | |
| SBwoT | 28 | 6.5 | 1.04 | 0.96-1.12 | <1.0 | 0.78 | 4 (14.2) | |
| SBwT | 35 | 7.9 | 1.44 | 1.33-1.55 | 39.8 | < 0.001 | 13 (37.0) | 0.05 |

NRMB Children with normal bladders
SBwoT Children with SB without trabeculation
SBwT Children with SB and trabeculation

B. Large Retrospective Study

After the initial pilot study, a larger retrospective study was undertaken to confirm the findings in a more robust results and to include patient ultrasounds.

Demographic data for this group is listed in Table 2.

Table 2: Demographic data of patients with no evidence of neurogenic bladders and those with spina bifida with and without trabeculation.

| | Patients (n) | Ages (yrs) | *Gender n(%) |
|--------------|-------------------------|-----------------------|-------------------------|
| NRMB | 75 | 3.0 | 53(71) |
| SBwoT | 71 | 6.71 | 32(45) |
| SBwT | 98 | 7.90 | 52(53) |

* Number and percentage of female patients

NRMB Children with normal bladders
SBwoT Children with SB without trabeculation
SBwT Children with SB and trabeculation

The cohort of patients with normal bladders included all patients who had an ultrasound and a VCUG within a two week period between January 2008 and May 2014. From this search query, 1296 patients were captured, of which 125 patients were chosen at random to represent the larger group. Of the 125 sample patients in

the identified larger group, 75 had normal VCUGs, with no evidence of vesicoureteral reflux or trabeculation. BDR for these patients was 1.09 (SD 0.13, 95% CI 1.06-1.12).

For the larger group of patients with spina bifida, all patients who had imaging between January 2008 and May 2014 with a diagnosis of spina bifida or neurogenic bladder, who underwent either a VCUG or video urodynamics and an ultrasound with 2 weeks of each other were reviewed. Of the 215 patients that were reviewed over this time period, 168 were included. Patients were excluded if they had previous surgery or imaging that could not be reviewed to calculate BDR on ultrasound and VCUGs or video urodynamics. The mean BDR for the entire groups was 1.41 (SD 0.44, 95% CI 1.34-1.48), which was statistically different than the BDR for the cohort of patients with normal bladders using a Student's t-test, $p < 0.001$.

Patients with spina bifida were then stratified into those with trabeculation and those without trabeculation on a VCUG or video urodynamics. Mean BDRs for the 3 groups were compared. Mean BDR for those patients with spina bifida and no trabeculation was 1.08 (SD 0.17, 95% CI 1.04-1.12), which was not statistically significant than the BDR for the patients with normal bladders, $p = 0.87$, representing a difference of less than 1%. Mean BDR for those patients with spina bifida and trabeculation was 1.64 (SD 0.43, 95% CI 1.55-1.73), which was statistically different than those patients with spina bifida and without trabeculation, $p < 0.001$.

The presence of upper tract pathology, denoted by the presence of vesicoureteral reflux or hydronephrosis was also evaluated in those patients with spina bifida. 23(32.4%) patients in the patients with spina bifida and trabeculation were found to have upper tract pathology, compared to 64(67.4%) patients in the group with spina bifida and trabeculation representing a statistically significant difference using a Fisher's Exact test ($p < 0.001$). A similar comparison with patients with normal bladders was made with those patients with spina bifida and no trabeculation, however this should be interpreted with caution since they were only included in the analysis if they had a normal VCUG and would have been excluded if vesicoureteral reflux was identified. For these patients, the presence of hydronephrosis alone in patients with normal bladders and those with spina bifida and no trabeculation was similar, 20(26.7%) and 19(27.1%) respectively.

The data are summarized in Table 3.

Table 3: Summary of BDRs and upper tract findings for patients with no evidence of neurogenic bladders and those with spina bifida with and without trabeculation.

| | Patients (n) | BDR | 95% CI | % Change | p Value | Upper Tract Changes n (%) | p Value |
|--------------|--------------|------|-----------|----------|-------------------|---------------------------|---------------------|
| NRMB | 75 | 1.09 | 1.06-1.12 | | | 20(26.7) | |
| SBwoT | 70 | 1.08 | 1.04-1.12 | <1.0 | 0.87 | 23 (32.4) | |
| SBwT | 98 | 1.64 | 1.55-1.73 | 51.8 | < 0.001 | 64 (67.4)** | <0.001*** |

* Patients with normal bladders and any hydronephrosis only

** 64/94 was used to calculate percentage as not all patients had ultrasounds

*** Fisher's Exact test

NRMB Children with normal bladders

SBwoT Children with SB without trabeculation

SBwT Children with SB and trabeculation

After evaluating BDR on VCUGs and video urodynamics, the evaluation of BDR on ultrasound was examined. Since trabeculation was a key dichotomizing variable, correlation between the presence of presence of trabeculation on VCUG and the observed presence of trabeculation ultrasound was performed and there was a positive correlation which was statistically significant, using a Pearson's correlation ($R = 0.41, p < 0.01$).

The level of agreement between the two imaging modalities was also examined using Cohen's kappa coefficient. Cohen's kappa coefficient for the measure of agreement between the two imaging modalities was 0.35, with a statistically

significant p value of <0.05 , which according to Landis and Koch's landmark papers, suggests a fair to moderate level of agreement.(Landis & Koch 1977a; Landis & Koch 1977b)

Since there appeared to be fair to moderate agreement between ultrasound and VCUG for all patients with spina bifida, BDR on ultrasound was assessed. There were 72 patients with normal bladders and 164 patients with spina bifida that had complete ultrasounds. Spina bifida patients were stratified into those with and without trabeculation. Patients with normal bladders had a BDR on ultrasound that was 0.95(SD 0.27, 95% CI 0.89-1.01). Of patients with spina bifida, 70 patients had no trabeculation and a BDR on ultrasound of 1.02 (SD 0.35, 95% CI 0.94-1.10) whereas the 94 patients with complete ultrasounds with spina bifida and trabeculation had a BDR of 1.32 (SD 0.41, 95% CI 1.24-1.40). There was no statistically significant difference in BDR on ultrasound for patients with normal bladders and those patients with spina bifida and no trabeculations, whereas there was a statistically significant difference between those patients with and without trabeculation, $p = 0.19$ and $p < 0.001$ respectively on Student's t-test.

Data has been summarized in Table 4.

Table 4: Summary of BDRs on ultrasound for patients with no evidence of neurogenic bladders and those with spina bifida with and without trabeculation.

| | Patients (n) | BDR | 95% CI | % Change | p Value |
|--------------|-------------------------|------------|---------------|---------------------|-------------------|
| NRMB | 72* | 0.95 | 0.89-1.01 | | |
| SBwoT | 70 | 1.02 | 0.95-1.11 | 7.4 | 0.19 |
| SBwT | 94* | 1.32 | 1.24-1.40 | 29.4 | < 0.001 |

*not all patients had completed ultrasounds

NRMB Children with normal bladders
SBwoT Children with SB without trabeculation
SBwT Children with SB and trabeculation

A separate analysis was performed stratifying patients with spina bifida based on whether trabeculation was detected on ultrasound and the BDR was evaluated. Mean BDR for patients with spina bifida and no trabeculation on ultrasound was 1.09 (SD 0.39, 95% CI 1.02-1.16), which was statistically significantly different to that seen on seen in patients with spina bifida and trabeculation on ultrasound, 1.44 (SD 0.35, 95% CI 1.34-1.54), $p < 0.001$.

SECTION 4: DISCUSSION

What Has Been Learned and Where Do We Go From Here?

The medical paradigm has been shifting significantly over recent decades. Medicine has transformed its view to one that identifies specific individuals among a population at risk and attempts to tailor treatment based on an individual's unique, and often subtle, risk factors. Ideally, there would be a specific treatment for each individual that encompasses his or her own unique biological, socio-economic and psychological factors and experiences, despite a similar diagnosis between individuals within a group.

When looking at a population with a wide spectrum of disease presentations and risk factors, such as the spina bifida population, it is even more crucial to appreciate the interplay of all these factors since historically, this patient population has been marginalized, over-treated, under-treated and for lack of a better phrase, simply poorly understood. In a population with so many "moving-parts", and "variables to the equation", any new factor that can be used by the clinician to lessen the burden of care and invasiveness of the treating these patients, care with is often life-long, is of the utmost importance. Here, a novel factor has been studied in patients with spina bifida and neurogenic bladder to help clinicians, families and patients guide care and hopefully do so in a less invasive manner.

Bladder diameter ratio was used to help describe what a normal bladder "looks like" on a VCUG and an ultrasound. In this work, BDR for patients with normal bladders and no clinical evidence of the presence of neurogenic bladder pathology was close

to 1 on both ultrasound and VCUG. The same was found for patients with spina bifida and no trabeculation with no statistically significant difference for this group when compared to the patients with normal bladders on either study. When looking at both these groups, the rates of upper tract pathology was also no statistically significant difference, although this finding may be interpreted with caution as a prerequisite for inclusion in to the group of patients with normal bladders was a normal VCUG, which would automatically exclude them from the study if they had vesicoureteral reflux. With that in mind, rates of hydronephrosis only in both groups was similar, suggesting that it would be reasonable to consider these groups as similar.

The statistically significant difference in BDR on both VCUG or video urodynamics and ultrasound in patients with spina bifida and trabeculation contrasts the findings in both groups and was also associated with a statistically significant increase of upper tract pathology in this group when compared to the patients with spina bifida and no trabeculation. This comparison included both vesicoureteral reflux and hydronephrosis in the analysis and the difference was quite remarkable.

When looking at the BDR on VCUG of the patients with normal bladders in the initial pilot study and those patients in the larger retrospective study, there was a slight difference in the calculated mean BDR, 1.03 versus 1.09 respectively. Although these patients were drawn from a difference time period, one would expect that the BDR in both these groups would be similar. This difference, which was approximately

5%, may reflect normal variation inherent in any study and could be explained by variation in measuring by the expert viewer or may in fact reflect no significant difference between the two results as the 95% confidence intervals overlap. This was further supported by the mean BDR for patients with normal bladders on ultrasounds, which was also close to 1.

These results should be further explored in a subsequent work where the measurement of BDR and agreement between different viewers will be further evaluated in a group of expert viewers to identify the inter-rater reliability of measuring BDR on a series of images. Here, one reviewer examined all images to calculate BDR.

Taken together it may be more appropriate to state a range for BDR. This too will be further examined in subsequent studies.

Regardless of the explanation for the slight measured differences in BDR across ultrasound and contrast studies, it can be confidently stated that the BDR for patients with normal bladders or those with spina bifida with no trabeculation is close to 1 and findings other than these may suggest an increased risk of upper tract pathology.

An interesting finding when looking at the demographic data of the larger retrospective study is the disproportionately higher number of females in the group

of patients with normal bladders. There was much closer gender equality in the patients with spina bifida, regardless of the presence of trabeculation, which would be expected. The increased number of females in the cohort of patients with normal bladders may reflect some element of selection bias since the, which would comprise a significant number of patients who had a VCUG as part of the workup for one or more urinary tract infections. It is widely known that beyond 6-12months of life, females have a significantly higher risk of developing urinary tract infections than males. This is can be seen in Table 5 which was adapted from the book by Baskin et al.(Baskin & Kogan 2005)

Table 5: Gender ratio of urinary tract infections by age.

| | Girls | Boys |
|---------|-------|------|
| Neonate | 0.4 | 1.0 |
| 1-6 mo | 1.5 | 1.0 |
| 6-12 mo | 4.0 | 1.0 |
| 1-3 y | 10.0 | 1.0 |
| 3-11 y | 9.0 | 1.0 |
| 1-16 y | 2.0 | 1.0 |

Part of the methodology of this study was to include stratify patients based on the presence of trabeculation on VCUG and then analyze the mean BDRs for dichotomized patients with spina bifida. If ultimately the goal of this study is to use ultrasound as the non-invasive diagnostic modality of choice to follow these patients with spina bifida long term, or least to reassure the clinician and family that the need for more invasive testing, given a reassuring intercurrent period of time

between visits, is unlikely to yield any concerning findings, then how well trabeculation is detected on ultrasound should be assessed.

A separate analysis to measure BDR based on the presence of trabeculation on ultrasound, as detected by a radiologist, was performed. Although there were a lower number of patients that were diagnosed with trabeculation for the analysis, 117 compared to 70 that were found to have trabeculation on the VCUG, the mean BDRs were identical at 1.09, although the patients stratified by trabeculation based on ultrasound had a higher standard deviation and wider confidence intervals. This reinforces the finding that BDR may reflect an objective and quantifiable deviation from what a normal urinary bladder may appear to be on ultrasound or contrast study and that significant increases in BDR may be linked to deterioration of the upper urinary tract.

For the calculation of BDR on contrast studies, attempts were made to capture the image that best reflected the maximal cystometric capacity of the bladder, which is generally a standard image acquired during VCUG or video urodynamics. As mentioned earlier, patients were excluded if these images were not obtained during the contrast study. When the BDR on the ultrasound was calculated, the corresponding measurements were made and BDR was calculated. One stark difference the presence of significantly under filled bladders during many of the ultrasound. In fact, for the patients with normal bladders, no patients had a calculated volume that was within 20% of the expected bladder capacity, using the

Koff formula.(Koff 1983) A similar finding was seen when evaluating the patients with spina bifida, where only 5 patients out of the entire group had calculated volumes at time of ultrasound within 20% of the theoretical expected bladder capacity.

There could be several factors at play to explain this finding, in that the calculated volume at time of ultrasound could have grossly underestimated the volume and in fact a greater number of patients may have actually had a larger volume in their bladder at time of ultrasound. Ultrasound is known to be a very operator-dependent imaging modality and there could be significant variability in the acquisition of the images. It was not possible to have ultrasound performed by a single technician and so it may be unlikely that all technicians would underestimate the bladder volume at time of ultrasound. One might expect to see some variability in both over and under estimating the bladder capacity, however it was consistently found that the bladder volume was very different than the predicted theoretical capacity. The corollary is that the formula that is used to calculate the volume, despite being widely used in the literature, may be an inaccurate estimation of the expected capacity.(Martínez-García et al. 2014)

In any event, the very fact that BDR is a ratio which may be stable as the bladder fills could explain why the measures were similar across imaging modalities and between the initial and then larger retrospective study. The conserved BDR ratio for a given bladder may remain constant, or least may begin to stabilize once the

bladder reaches a certain percentage-fill. Needless to say, there is still much to be studied from this new and possible first objective descriptor of normal bladder shape.

Whatever the cause of the significant variation in the calculated volume at the time of ultrasound, it has prompted the undertaking of a prospective study to better accurately gather data that is of better quality and to better approximate what the measures intend to reflect. To this end, a proposal has been written and put forth to the institutional review board for collection of prospective data. The proposal has been accepted and prospective patient data is due to be collected over the coming months. For this study, an ultrasound will be performed at the time of video urodynamics and so the exact volume of fluid in the bladder will be known as it will be artificially filled. A more accurate comparison can be made with regards to the calculation of the BDR on both imaging modalities for measurements of BDR height and width.

Limitations to the Study

For the above-mentioned prospective study, several of the variables listed in the methods section under domain of observables will be collected. Attempts were made to gather data on bladder pressures and several other factors to see their effect on BDR, however oftentimes data was incomplete and difficult to glean from chart review. Some of these issues will be addressed during the prospective study.

With this in mind there were several limitations to the study, which warrant discussion.

A major criticism of this work may be its retrospective nature. As mentioned, some data was incomplete during chart review and some patients needed to be excluded from the study. Also, certain ultrasounds could not be used in the calculation of BDR for some patients, in all 4, as bladders were empty at the time of ultrasound and no BDR could be calculated. As mentioned earlier, it would be quite important to correlate bladder pressures to BDR, as this is also a key measure of bladder stability. Some work on this has already been done by our group (data not yet published), however this will also be looked at in the prospective study.

Although BDR is a ratio and may be constant with bladder filling and may be independent of patient body habitus, there may be some slight variation that depends on the age or size of the patient. Although age was captured, weight and linear height were not measured and it may be helpful to examine the impact of these variables on BDR and to further specify what is normal. If there are large deviations from this expected ratio in any particular group based on age or bladder volume, regression analysis can be performed to identify the exact increase (or decrease) in BDR per unit age or bladder volume. This would be a suitable method to validate the instrument for this population over a variety of age ranges and bladder volumes. A nomogram can be created to predict the estimated BDR for age and bladder volume in this situation.

The thickness of the bladder wall may also affect the measurement of BDR on ultrasound, as the viewer needs to be able to see the interface between the bladder wall and vesicular fluid. Although a possible confounder, it is expected to impart minimal variation in BDR measurement if the bladder is filled and volume is known.

SECTION 5: SUMMARY

This is possibly the first study to evaluate objective measures of what constitutes normal bladder shape, as defined by the bladder diameter ratio. It describes what constitutes normal bladder shape in children without evidence of neurogenic bladders and helps to understand the link between changes in bladder shape in children with spina bifida based on a known marker of disease progression, trabeculation. Correlates to upper tract pathology confirmed the clinical usefulness of BDR as there were increase in the presence of upper tract pathology in the group with a high mean BDR, reinforcing the link between trabeculation, BDR and upper tract changes pathology. Although this is a retrospective study and further work is required to confirm these findings in a group of patients with data collected prospectively, this data appears promising in helping clinicians treat patients with a tailored approach and potentially with less invasive and resource-sparing investigations, without compromising safety.

More research is needed to better understand the relationship between bladder shape and clinical outcomes. This work shows promise for future prospective studies that may be able to answer the questions posed here.

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