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A Possible Use of Color Doppler Flow Imaging in Predicting the Cause of Bladder Hypertrophy

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Naya, Y. *A Possible Use of Color Doppler Flow Imaging in Predicting the Course of Bladder Hypertrophy.* Tohoku J. Exp. Med., 1997, **182** (2), 139-150 —— The present study was designed to test the predictability of color Doppler flow imaging of the bladder in determining the cause of bladder hypertrophy. The blood flow in the anterior bladder wall was measured in 35 patients with an abnormally increased ultrasound estimated bladder weight (UEBW) of more than 35.0 g. Of these, 18 were diagnosed as having infravesical obstruction due to benign prostatic hyperplasia (obstructive group). The remaining 17 were diagnosed as having neurogenic bladder dysfunction (NB group). Scanning to detect blood flow was continued for 5 minutes, the bladder having been filled with 100 ml of saline. Blood flow was detected in 83.3% (15/18) of the obstructive group, compared to 23.5% (4/17) in the NB group ($p<0.001$). Infravesical obstruction was detected with a diagnostic accuracy of 80.0% (28/35) by color Doppler flow imaging. Color Doppler flow imaging was useful in predicting the cause of bladder hypertrophy in patients with abnormally increased UEBW.
———— color Doppler flow imaging; benign prostatic hyperplasia; infravesical obstruction, Neurogenic bladder dysfunction; ultrasound estimated bladder weight

It is well known that infravesical obstruction is followed by compensatory hypertrophy of the detrusor in human and animal bladders (Brent and Stephens 1975; Mattiasson and Uvelius 1982; Ghoniem et al. 1986; Walsh 1992). Recently, reports have been published on ultrasound estimated bladder weight (UEBW), which increased significantly in men with infravesical obstruction such as benign prostatic hyperplasia (BPH), prostatic cancer and urethral stricture, compared with men with no infravesical obstruction (Kojima et al. 1996a, b). On the other hand, UEBW was also shown to increase abnormally in some patients suffering from neurogenic bladder dysfunction with detrusor areflexia, indicating a significant correlation with the compliance and the deformity of the affected bladder (Kojima et al. 1996c).

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Thus, it may be possible that there are at least two causes of bladder hypertrophy. The present study was based on the assumption that there might be some difference in blood perfusion between hypertrophic bladders accompanied by infravesical obstruction and those with neurogenic bladder dysfunction. The ability of color Doppler flow imaging of the bladder to predict the cause of bladder hypertrophy was tested in this study.

Materials and Methods

Between August, 1995, and March, 1996, the blood flow in the bladder wall was measured in 35 patients (30 males and 5 females) with an abnormally increased UEBW of more than 35.0 g. Their ages ranged from 20 to 88 years, with a mean of 67.7 $\pm$ 14.2 years. Of these cases, 18 were diagnosed as having BPH by transrectal sonography (obstructive group) (Watanabe et al. 1975; Watanabe 1993). By pressure flow studies, they were all confirmed as having infravesical obstruction. The remaining 17 patients (12 males and 5 females) were diagnosed urodynamically as having neurogenic bladder dysfunction with an underactive detrusor (NB group). Pressure flow studies proved no infravesical obstruction in all male patients of this group. The blood flow was also measured in 10 patients (7 males and 3 females) with normal UEBW of less than 35.0 g. Their ages ranged from 25 to 79 years, with a mean of 62.2 $\pm$ 15.2 years. They had neither urinary symptoms nor a past history suggestive of the presence of neurogenic bladder dysfunction and infravesical obstruction (control group).

UEBW was measured according to the method reported previously (Kojima et al. 1996a). In short, transabdominal ultrasonography was performed on patients in the supine position using 7.5 MHz probe (PLF-703ST, Toshiba, Tokyo). We used a probe of high frequency (7.5 MHz), because the observation of the anatomic fine features of the three layers in the bladder wall could be possible.

A longitudinal scan was obtained on the midline of the lower abdomen just above the pubic synthesis. The thickness of the anterior wall was measured at three points, of which the average was recorded as the thickness of the bladder, a catheter was inserted into the bladder to measure the volume of urine it contained. From the thickness of the anterior bladder wall, measured ultrasonically, and the intravesical volume, bladder volume was calculated supposing the bladder to be a sphere. Since the specific gravity was nearly equal to 1.0, the calculated bladder volume was defined as the UEBW (Fig. 1).

Since a significant decrease in blood flow with bladder distension was reported in animals (Dunn 1974; Finkbeiner and Lapides 1974; Nemeth et al. 1977) and elevated intravesical pressure could considerably affect the results of color Doppler flow imaging, prior to color Doppler flow imaging of the bladder wall, filling cystometry was performed with a catheter inserted through the urethra, using CO_2 gas as a medium, at a filling rate of 50 ml/min (Cystometry Unit Type 21G01,

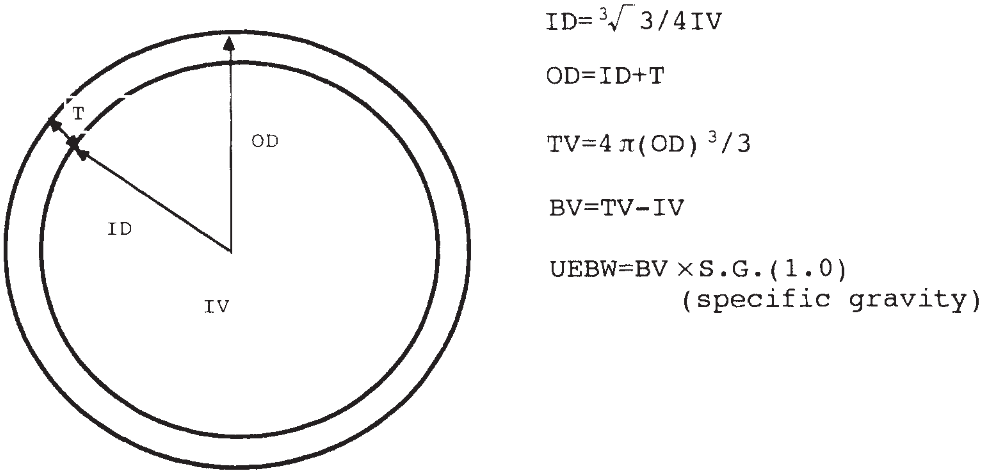

Fig. 1. Schematic drawing of calculation of the UEBW, assuming spheric bladder. ID, inner diameter; OD, outer diameter; T, bladder wall thickness (measured); BV, bladder wall volume; IV, intravesical volume (measured).

DISA, Skovlunde, Denmark). The intravesical pressure at 100 ml of CO_2 infused (IVP_{100}) was recorded. The maximum cystometric capacity was determined when patients had the maximum desire to void, or when there was a leak around the catheter. Filling was stopped when the gas volume reached 500 ml, because to continue would have been harmful to the bladder.

The bladder was filled again with 100 ml of sterilized saline to keep intravesical volume constant. The anterior bladder wall was scanned transabdominally using a 7.5 MHz probe (PLF-703ST) and an ultrasound machine (Sonolayer SSA-270A, Toshiba). Scanning to detect blood flow was continued for 5 minutes, and the results were classified into two categories. BF(+) when blood flow was detected and BF(−) when it was not. The lowest velocity of the blood flow detected using this ultrasound apparatus was 1 cm/sec. In the BF(+) cases, blood flow was classified into pulsatile or non-pulsatile waves. When blood flow was detected, maximum (V_{max}) and minimum (V_{min}) blood flow velocities were measured by the pulsed-Doppler method. In the measurement of V_{max} and V_{min}, the angle of interrogation of the ultrasound beam related to the vessel was not corrected. In patients with pulsatile blood flow, the resistive index (RI) was calculated ($RI = V_{max} - V_{min}/V_{max}$). Values were expressed as the mean plus or minus standard deviation. Statistical analyses were performed using Fisher's exact value and Mann-Whitney U-test. A *p*-value of less than 0.05 was defined as statistically significant.

Results

There was no significant difference in age, UEBW and IVP_{100} between the obstructive and the NB groups (Table 1). Cystometric bladder capacity was significantly larger in the NB group than in the obstructive group ($p < 0.05$).

Blood flows were detected in neither males nor females of the control group

TABLE 1. *Comparison of measurements between patients with infravesical obstruction and neurogenic bladder dysfunction*

	Obstructive group ($n=18$)	NB Group ($n=17$)	Statistics[a]
Age (years)	53-83 (70.3±7.2)	20-88 (64.9±18.8)	n.s.
UEBM (g)	35.9-126.6 (62.4±27.5)	35.6-104.4 (60.0±21.9)	n.s.
IVP_{100} (cmH_2O)	1 10 (4.9±2.8)	1-22 (5.9±6.5)	n.s.
Cystometric bladder capacity (ml)	100-375 (193.3±71.9)	110-500 (280.8±119.1)	$p<0.05$
V_{max} (cm/sec)	2-20 ($n=15$) (8.2±4.7)	2-10 ($n=4$) (7.3±3.6)	n.s.
V_{min} (cm/sec)	1-5 ($n=15$) (2.0±1.2)	1-3 ($n=4$) (2.0±0.8)	n.s.
Resistive index	0.677-0.950 ($n=11$) (0.796±0.090)	0.500-0.777 ($n=4$) (0.682±0.125)	n.s.

[a]Mann-Whitney U-test
Ranges ase shown with mean±S.D. in parentheses.
Number of the subjects is indicated following the range when necessary.
n.s., not significant

(Fig. 2). The detection of blood flows was significantly more frequent in the obstructive group than in the NB group ($p<0.001$). The percentage of BF(+) and BF(−) was 83.3% (15/18) and 16.7% (3/18), respectively, in the obstructive group. In contrast, the percentage of BF(+) and BF(−) was 23.5% (4/17) and 76.5% (13/17), respectively, in the NB group. Similarly, 15 (78.9%) of 19 patients with BF(+) belonged to the obstructive group (Figs. 3 and 4), while 13 (81.2%) of 16 patients with BF(−) belonged to the NB group (Fig. 5). As a result, infravesical obstruction could be predicted with a diagnostic accuracy of 80.0% (28/35) using color Doppler flow imaging. False positive and negative rates were 21.1% (4/19) and 18.8% (3/16), respectively (Table 2). In obstructive group, no significant difference was found in UEBW between patients with BF(+) and those with BF(−). The number of blood vessels detected was one in 14, two in 4 and three in 1. There was no significant difference between the number of blood vessels.

In 16 (84.2%) out of 19 patients with BF(+), pulsatile blood flows were confirmed by the pulsed-Doppler method (Fig. 3). Non-pulsatile blood flow was observed in the remaining 3 patients (15.8%), who were all of the obstructive group (Fig. 4). Comparing V_{max}, V_{min} and RI obtained from the pulsed-Doppler method in these 16 patients between the obstructive and NB groups, there was no significant difference (Table 1). On the other hand, comparison between patients with BF(+) and BF(−) revealed that the former had significantly higher IVP_{100}

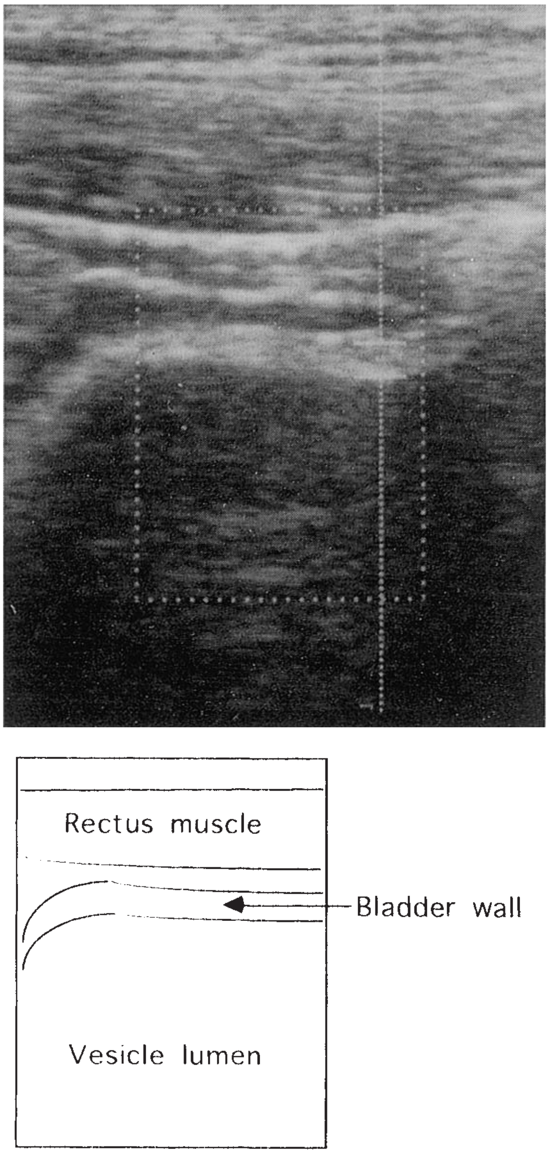

Fig. 2. Transabdominal sonogram of anterior bladder wall of 33-year-old patient with male infertility (control group). No blood flow was detected.

and less cystometric bladder capacity than the latter ($p<0.05$) (Table 3).

Discussion

As reported previously, UEBW is considered to be of value as a quantitative measurement of bladder hypertrophy in clinical settings (Kojima et al. 1996a). Furthermore, its significant correlation with the severity of infravesical obstruction as evaluated by pressure flow studies suggests its clinical usefulness in the diagnosis of the obstruction (Kojima et al. 1996b). Although UEBW could correctly predict infravesical obstruction in 86.2% of patients suffering from urinary symptoms, 12.1% of them were false positive. On the other hand, UEBW was demonstrated to increase abnormally in patients with neurogenic bladder dysfunction, showing a significant correlation with bladder compliance and deformity (Kojima et al. 1996c). Thus, bladder hypertrophy, which was recog-

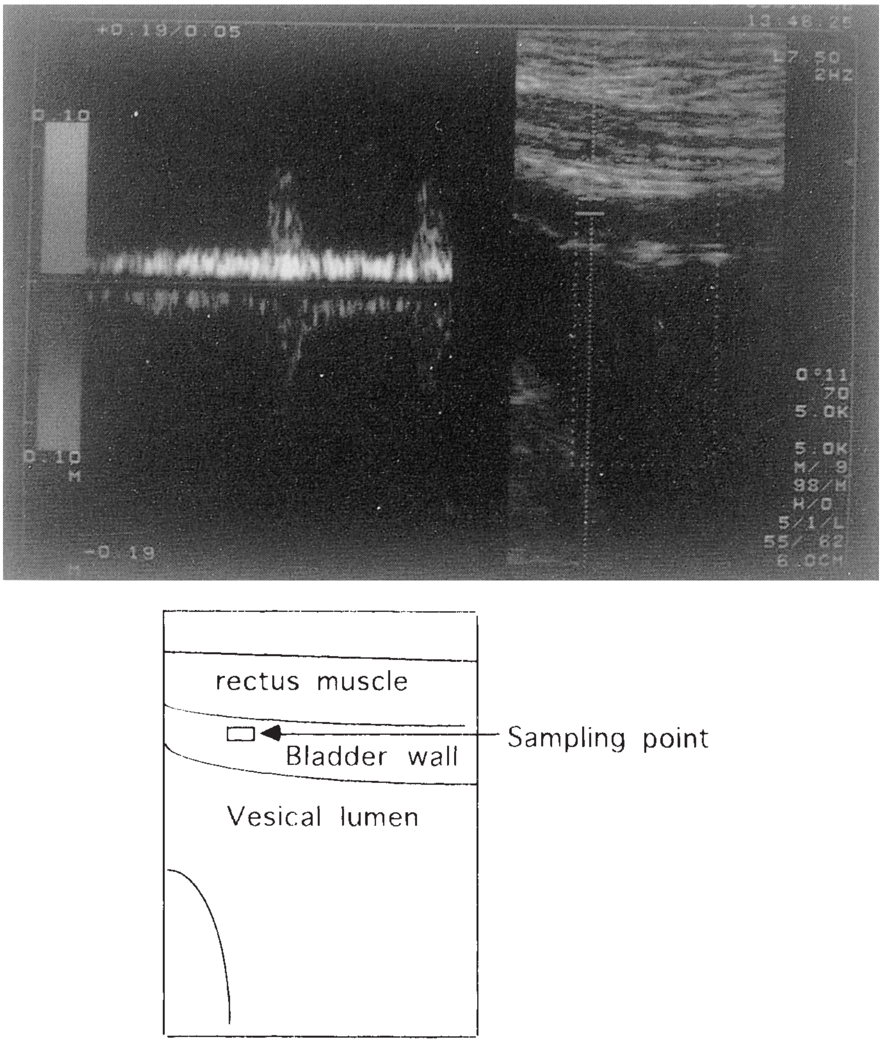

Fig. 3. Color Doppler flow image of the anterior bladder wall in a 64 year-old male patient with infravesical obstruction due to benign prostatic hyperplasia. The ultrasound estimated bladder weight was 47.4 g. The sound spectrogram showed a pulsatile blood flow.

nized by an abnormally elevated UEBW, could be caused by neurogenic factors as well as infravesical obstruction. It is therefore of necessity to establish a method which can correctly distinguish the cause of bladder hypertrophy.

In the present study, patients having a UEBW of 35.0 g or more were evaluated by color Doppler flow imaging. That level of UEBW could be considered abnormal in terms of bladder hypertrophy for the following two reasons. First, the value of 35.0 g almost corresponded with that of a mean +2 s.d. (25.6± 5.7 g) in normal control men, as shown in our previous study. The UEBW in obstructive group was significantly greater (48 patients, 49.7±19.5 g) than that in the normal control group(41 patients, 25.6±5.7 g; $p<0.0001$) or the nonobstructed group (28.4±4.2 g; $p<0.0001$). The highest UEBW in the normal control and nonobstructed group was 34.8 g and 35.2 g, respectively, whereas 94% of obstructed group had a UEBW greater than 35.0 g (Kojima et al. 1996a). Secondly, our

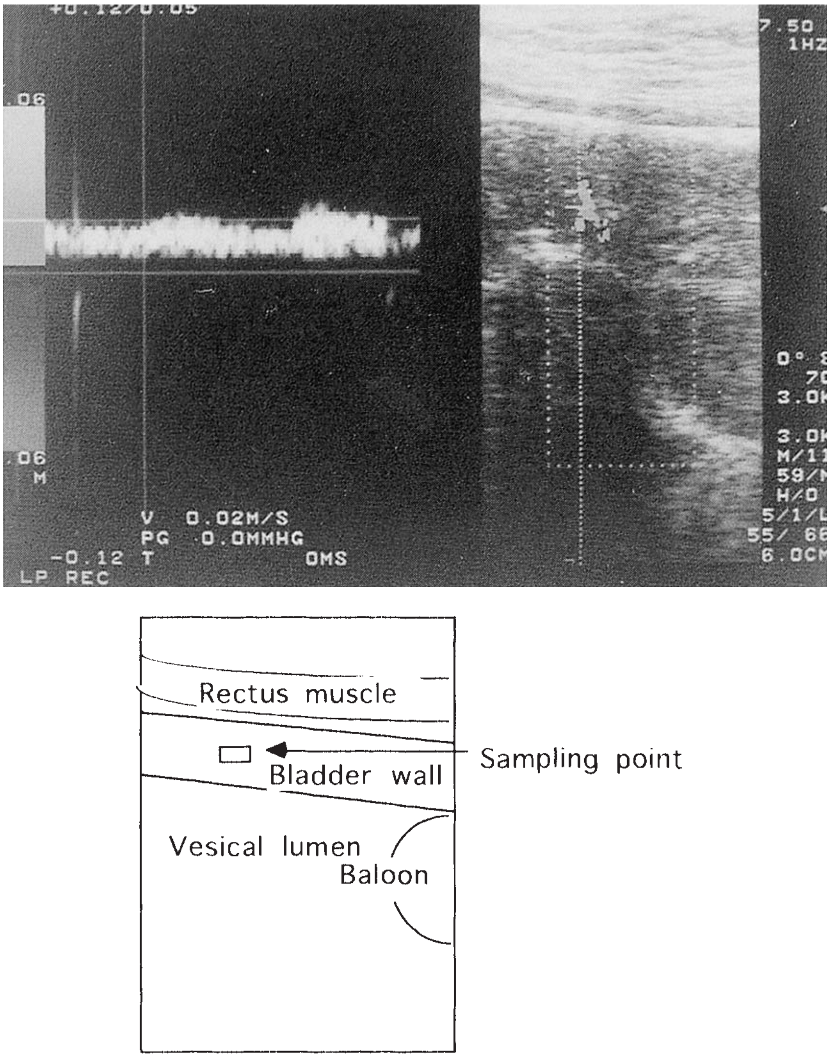

Fig. 4. Color Doppler flow image of the anterior bladder wall in a 68 year-old male patient with infravesical obstruction due to benign prostatic hyperplasia. The ultrasound estimated bladder weight was 95.7 g. The sound spectrogram showed a non-pulsatile blood flow.

previous study confirmed that 35.0 g was the most suitable cutoff value for UEBW in the prediction of infravesical obstruction as determined by pressure flow studies (Kojima et al. 1996b).

An experimental model in rats demonstrated that the bladder weight gain induced by infravesical obstruction was caused mainly by an increased thickness of the muscle layer with smooth muscle cell hypertrophy and/or hyperplasia of the detrusor (Uvelius et al. 1984). Similarly, Gilpin et al. (1985) clarified that in the human bladder smooth muscle cells also underwent compensatory hypertrophy in response to infravesical obstruction. Although histopathological changes in the hypertrophied bladder of patients with neurogenic bladder dysfunction remain unknown, it is likely that the underlying pathology of hypertrophied bladder is different between patients with infravesical obstruction and those with neurogenic bladder dysfunction.

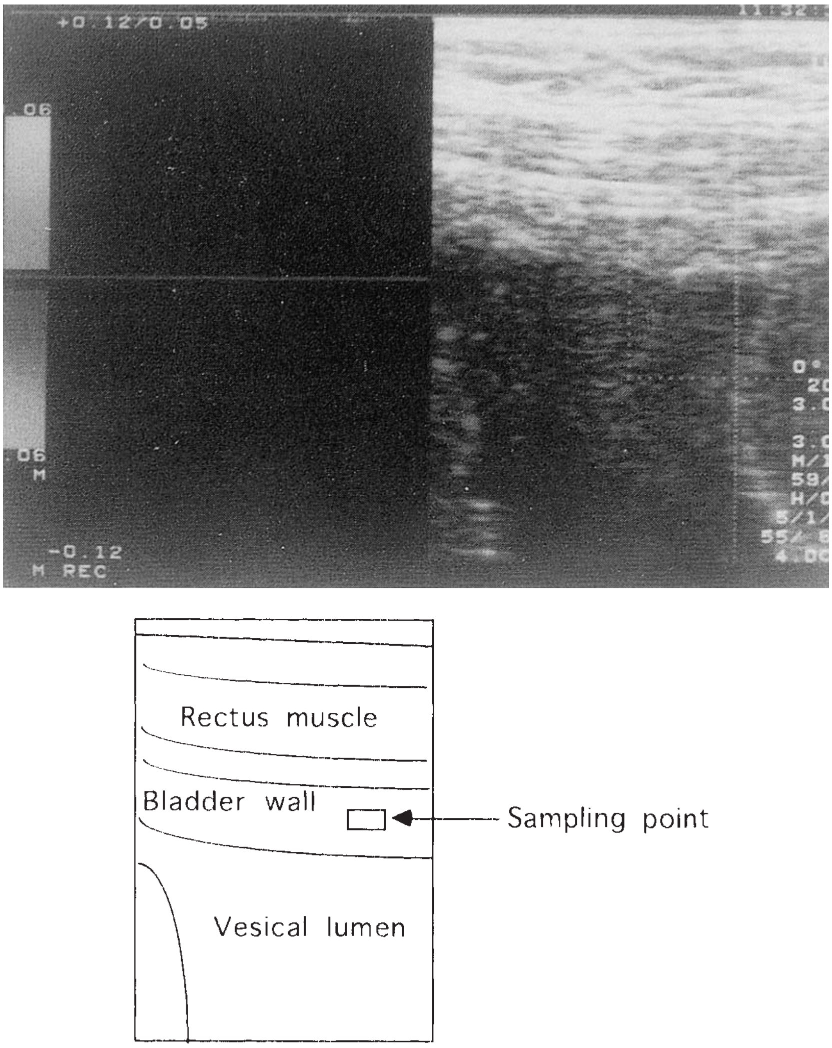

Fig. 5. Color Doppler flow image of the anterior bladder wall in a 71 year-old female patient with neurogenic bladder dysfunction with underactive detrusor. The ultrasound estimated bladder weight was 52.2 g. No blood flow was detected.

TABLE 2. *Diagnostic value of color Doppler flow imaging in the prediction of the couse of bladder hypertrophy*

Group	Obstructive group	NB Group	Total
BF (+)	15	4	19
(−)	3	13	16
Total	18	17	35
Sensitivity		83.8% (15/18)	
Specificity		76.5% (13/17)	
Positive predictive value		78.9% (15/19)	
Negative predictive value		81.2% (13/16)	
Diagnostic accuracy		80.0% (28/35)	

TABLE 3. *Comparison of measurements between patients with BF (+) and BF (−)*

	BF (+) ($n=19$)	BF (−) ($n=16$)	Statistics[a]
Age (years)	26-83 (66.6±13.2)	20-88 (68.9±15.5)	n.s.
UEBW(g)	35.9-126.6 (64.6±28.7)	35.6-101.6 (57.3±18.8)	n.s.
IVP_{100} (cmH_2O)	2-18 (6.2±4.0)	1-22 (4.4±5.8)	$p<0.05$
Cystometric bladder capacity (ml)	100-353 (197.3±74.5)	120-500 (281.6±121.1)	$p<0.05$

[a]Mann-Whitney U-test

BF (+), blood flow positive; BF (−), blood flow negative; UEBW, ultrasound estimated blodder weight; IVP_{100}, The intravesical pressure at 100 ml of CO_2 infused.

n.s., not significant

Blood flow perfusion has been investigated with radio-labeled washout techniques in rabbits (Dunn 1974) and dogs (Finkbeiner and Lapides 1974). In clinical studies, Irwin and Galloway (1993) introduced laser Doppler flowmetry to detect blood flow perfusion in the human bladder. More recently, Batista et al. (1996) measured blood flow in the human bladder directly using laser Doppler flowmetry. Throughout these studies, blood perfusion of the bladder has been discussed particularly in terms of the relationship to bladder function. Diminished blood perfusion caused impaired bladder function. Gill et al. (1988) demonstrated a 72% decrease of contractile response to bethanechol after unilateral vesical artery ligation and a 97% reduction after bilateral ligation. Although they did not assess blood perfusion, it may be likely that blood flow perfusion of the bladder decreases in patients having neurogenic bladder dysfunction with an underactive detrusor. The present study was designed on the assumption that blood perfusion in the hypertrophied bladder wall might be different between neurogenic disorders and infravesical obstruction.

In the last decade, remarkable improvements have been obtained concerning blood perfusion with the use of color Doppler flow imaging, which has made it possible to evaluate the status of blood flow non-invasively in many organs. This is the first study to apply color Doppler flow imaging to the bladder wall. The procedure is characterized by its non-invasiveness and ease of application.

A statistically significant decrease in blood flow with bladder distension was confirmed using radio-labeled markers in rabbits and dogs (Dunn 1974; Finkbeiner and Lapides 1974; Nemeth et al. 1977). Interestingly, Dunn (1974) reported a significant reduction of blood flow through the bladder wall in rabbits, showing that blood flow reduced to half that of a resting bladder when the bladder was distended by 20 mmHg of intravesical pressure, reduced to a quarter at a pressure of 40 mmHg, and to 1/20 when the intravesical pressure was raised to 80 mmHg. Finkbeiner and Lapides (1974) found in the dog bladder that mean flow rate of the bladder reduced from 21.24 ± 7.42 to 14.57 ± 4.01 ml/min/100 g tissue following bladder distension for 2 hours. In the human bladder, bladder filling was also demonstrated to result in reduced mean blood flow in the bladder wall (Batista et al. 1996). Thus, it is to be noted that the degree of distension and that of intravesical pressure could considerably affect the results of color Doppler flow imaging.

In our series of patients, the measurement of color Doppler flow imaging was performed with the bladder capacity constant (100 ml) but with IVP_{100} variable among patients. Importantly, there was a significant difference in IVP_{100} between patients with BF(+) and BF(−). It was unexpected, however, that IVP_{100} was significantly higher in patients with BF(+) than in those with BF(−). Considering the small difference in IVP_{100}, although statistically significant, between these two groups and the limited number of patients examined, it may be difficult to come to any conclusion on the relationship between intravesical pressure and color Doppler flow imaging in patients with bladder hypertrophy. Further studies are needed to reveal the relationship between blood perfusion as evaluated by color Doppler flow imaging and the distension of the bladder.

In the present study, blood flow was examined at the anterior bladder wall. Using laser Doppler flowmetry applied to the bladder on open surgery, Batista et al. (1996) demonstrated a regional variation in blood flow. In their study, blood flow was significantly higher in the dome than in the anterior wall in the empty bladder (15.5 ± 6.8 vs. 5.4 ± 2.2 ml/min/100 g tissue; $p < 0.001$). Blood flow reduction with the bladder filling was more significant in the dome than in the anterior wall. The anterior bladder wall as used in this study may be the most suitable site for the evaluation of blood flow with fewer effects from bladder filling.

The most striking feature in the present study was that blood flow could be detected more frequently in patients with bladder hypertrophy accompanied by infravesical obstruction than in those with neurogenic bladder dysfunction. Recently, Lin et al. (1995) reported using laser Doppler flowmetry in rabbits that 2 weeks after the induction of outlet obstruction bladder blood flow decreased significantly from 16.1 ± 0.7 $ml \cdot min^{-1} \cdot (100\ g\ tissue)^{-1}$ to 4.9 ± 1.2 $ml \cdot min^{-1} \cdot (100\ g\ tissue)^{-1}$ ($p < 0.05$). Putting our results together might demonstrate that blood perfusion in the bladder affected by neurogenic bladder dysfunction reduces more considerably compared to that in compensatory hypertrophic bladders caused by infravesical obstruction. More important is that color Doppler flow imaging can be used as a measure in the differential diagnosis of the etiology of bladder hypertrophy.

The status of blood flow as evaluated by color Doppler flow imaging might represent the histopathological as well as the functional changes of the bladder detrusor. Consequently, the combination of UEBW and color Doppler flow imaging could be promising in evaluating the pathophysiology of bladder hypertrophy.

Conclusion

Color Doppler flow imaging was useful in predicting the cause of bladder hypertrophy in patients with an abnormally increased UEBW of more than 35 g.

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