Non-Invasive Ultrasonic Diagnosis of Urinary Bladder Outlet Obstruction

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Colophon

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Doctoral dissertation, Erasmus Medical Center, the Netherlands

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Non-Invasive Ultrasonic Diagnosis of Urinary Bladder Outlet Obstruction

Niet-invasieve diagnose van urineblaasobstructie met
behulp van ultrageluid

Thesis

to obtain the degree of doctor from the
Erasmus University Rotterdam
by command of the rector magnificus

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PART I

GENERAL INTRODUCTION

Chapter 1

Introduction and outline of the thesis

1. Introduction

1.1 Urinary Tract

The urinary tract is divided into two parts, the upper urinary tract consisting of kidneys and ureters and the lower urinary tract consisting of bladder and urethra. The function of the upper urinary tract is to filter the blood and transport urine into the bladder into the lower urinary tract. During urination or voiding, the detrusor muscle of the bladder contracts which propels urine out of the bladder pass it via urethra out of the body. In man, the prostate is located around the urethra at its most proximal part.

1.2 Lower Urinary Tract Symptoms

With increasing age men often develop Lower Urinary Tract Symptoms (LUTS), such as post-void residual volume, low urinary flow rate, nocturia (frequent voiding at night), dribbling etc. These LUTS have a significant negative impact on the patient's quality of life. Benign Prostate Enlargement (BPE), a nonmalignant enlargement of the prostate most commonly causes such LUTS in elderly males (1). Over fifty years of age, around 68% men have histological evidence of prostatic enlargement (2, 3).

1.3 Bladder Outlet Obstruction

An enlarged prostate results in compression of the urethra and may cause Bladder Outlet Obstruction (BOO) as shown in Figure 1. Men with LUTS are often presumed to have BOO. However, the literature shows that the association between LUTS and BOO is uncertain (4). Weak detrusor muscle contractility can also cause LUTS in men.

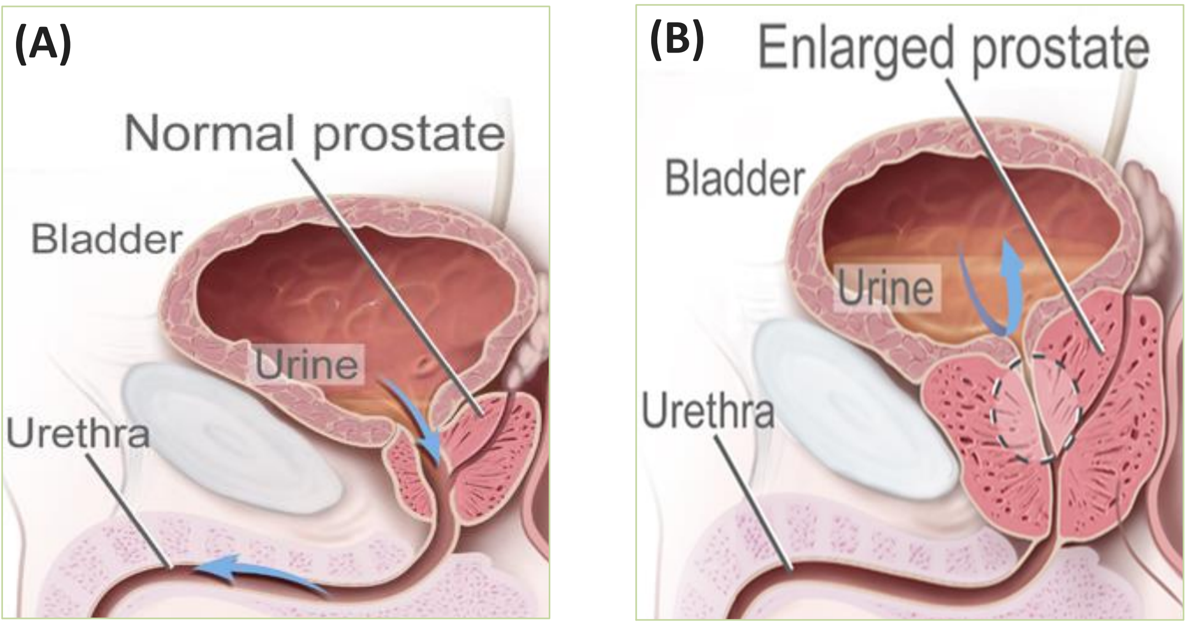

Figure 1: *Cross-section of (A) a normal prostate and (B) an enlarged prostate causing bladder outlet obstruction* (Image obtained from http://en.wikipedia.org/wiki/Benign_prostatic_hyperplasia).

1.4 The Standard Invasive Diagnostic Method

Pressure-flow studies measuring voiding detrusor pressure and urinary flow rate are the standard method for diagnosing BOO (5). In this diagnostic method, one double-lumen catheter or two single lumen catheters are inserted through the urethra into the urinary bladder, and a single-lumen catheter is inserted into the rectum (see Figure 2).

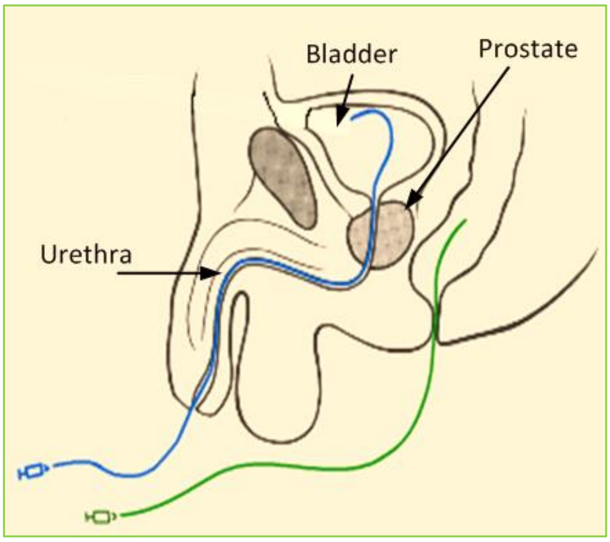

Figure 2: *Setup for an invasive pressure flow study. One double-lumen catheter (blue) is inserted into the urinary bladder via the urethra, and a single-lumen catheter (green) is inserted into the rectum (6).*

One lumen of the bladder catheter and the lumen of the rectal catheter are connected to pressure transducers to measure intravesical pressure, p_{ves}, and abdominal pressure, p_{abd} respectively, during filling and voiding. The other lumen of the bladder catheter is connected to a pump which fills the bladder with contrast fluid or saline.

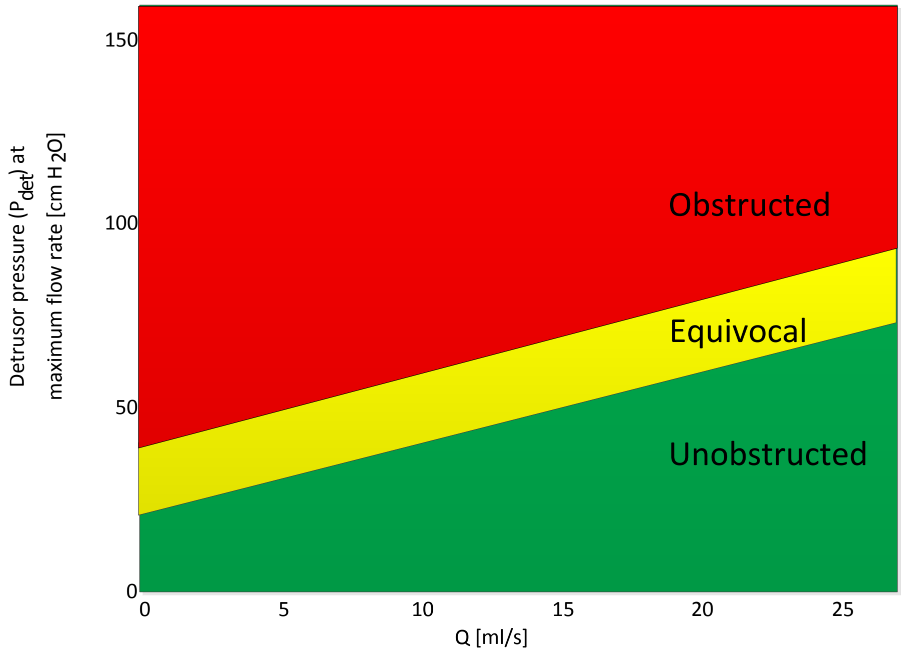

Figure 3: *A pressure flow nomogram to classify patients into obstructed, equivocal or unobstructed using pressure flow data.*

The flow rate, Q, is measured using an external flowmeter. From the maximum urinary flow rate Q_{max} and the detrusor pressure, $p_{det} = p_{ves} - p_{abd}$, measured at Q_{max}, the patient is diagnosed as obstructed, unobstructed or equivocal using a pressure flow nomogram (5) as shown in Figure 3. A major disadvantage of a pressure-flow study is that it involves urethral catheterization, which causes partial obstruction during urination and may alter the diagnostic result. The invasive nature of the method may also cause infection, pain and discomfort to patients.

1.5 Non-invasive Diagnostic Methods

Urodynamic experts have proposed a variety of non-invasive and more patient friendly diagnostic methods for BOO in patients with LUTS, such as the condom catheter method, the penile cuff method, perineal sound recording, ultrasonic measurement of bladder wall thickness and Doppler flowmetry (7-11). The condom catheter method and penile cuff method provide a non-invasive estimate of bladder pressure.

1.5.1 Condom Catheter Method: In the condom method, a modified incontinence condom which is connected to a pressure transducer is applied to the penis of the patient. During voiding the outflow of the condom is blocked and the channel between the condom and bladder is open, which enables a pressure measurement in the condom representing the bladder pressure (12). The technique can be used to differentiate between obstructed and unobstructed patients by combining the recorded pressure values with a separately measured urinary flow rate. However, the technique is less accurate at low flow rate values as successful pressure measurement requires that the condom is quickly filled and pressurized (13).

1.5.2 Penile Cuff Method: With the penile cuff method, a small inflatable cuff is placed around the penis similar to the method used for blood pressure measurement. During voiding the cuff is inflated until the urinary flow stops and the pressure in the cuff then represents a measure of the bladder pressure. This technique categorizes the patients into obstructed, unobstructed or equivocal groups by plotting the penile cuff pressure and maximum flow rate on a modified pressure-flow nomogram (14). However, the studies have shown that the patient cannot void freely (9, 15).

1.5.3 Perineal Sound Recording: Perineal sound recording is based on recording of sound produced by urinary flow during voiding using a contact microphone placed at the perineum. The method shows that urinary flow becomes turbulent due to BOO. The turbulence causes pressure variations at the urethral wall which can be recorded as sound using a microphone and are related to the degree of obstruction. An advantage of such a method is simplicity. However, the precise relation between perineal sound and the degree of obstruction could be influenced by the viscoelastic properties and thickness of the urethra and the tissues surrounding the urethra.

1.5.4 Bladder Wall Thickness Method: The measurement of changes in bladder wall thickness (BWT) using ultrasound has been proposed as a potential diagnostic tool of BOO. Manieri *et al.* (10) measured BWT at a constant bladder volume of 150ml in LUTS patients. A thickness of 5mm appeared to be the best cut-off value to diagnose BOO. However, another study (16) showed no significant difference in BWT in 150 men with LUTS and age-matched healthy persons at different bladder volumes.

1.5.5 Color Doppler Ultrasound: The Doppler effect refers to the change in frequency of a wave resulting from relative motion between the source of the wave and an observer. In diagnostic ultrasound, ultrasound waves of particular frequency are emitted from an ultrasound transducer. When these waves are reflected by moving scattering particles they return to the transducer with a different frequency where frequency shift is directly related to the velocity of the object (Doppler effect). In color Doppler ultrasound, this frequency shift between transmitted and received ultrasound signals is used to calculate flow velocity which can be presented as a color coded overlay on top of a ultrasound image (see Figure 4).

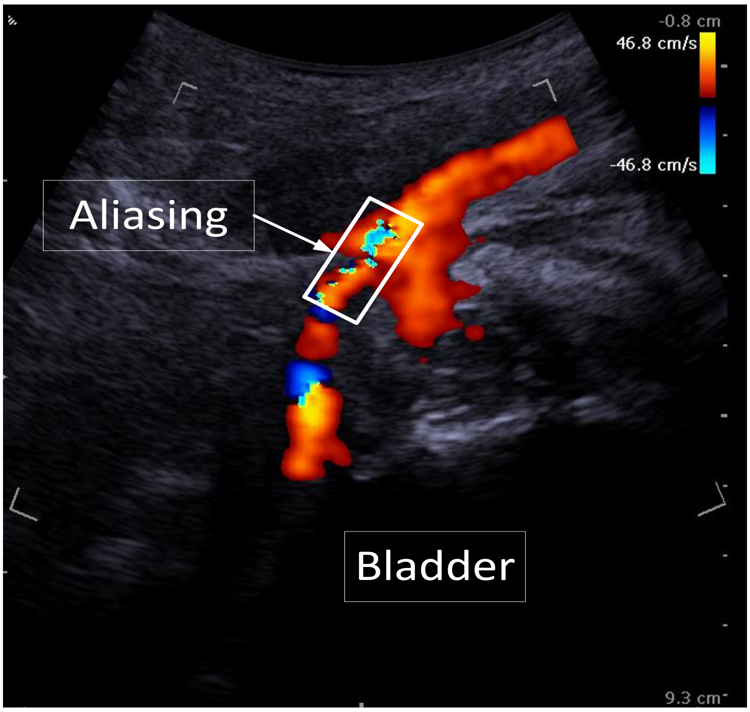

Figure 4: *A color Doppler ultrasound image of urinary flow in a healthy male. The colorbar represents the measured urine flow velocity. The maximum scale for velocity measurement was at 47cm/s. Red and blue colors represents flow towards or away from the transducer. In the flow an aliasing effect can be seen due to the high urine flow velocity.*

Color Doppler ultrasound can also be used to measure urinary flow velocity in the urethra. In a urethra model study (17) it was shown that the changes in flow velocity are related to pressure variations which cause dissolved gas in the urine to form microbubbles in the prostatic urethra . These microbubbles act as scattering particles which reflect ultrasound signals and can be used for measuring the Doppler effect. A remote controlled robotic probe holder was used to measure urine flow velocity transperinealy in the distal prostatic urethra just above the external sphincter and in the sphincteric urethra. The ratio of the two measured flow velocities was used to diagnose BOO in patients. In a study of 22 men, a velocity ratio cut-off point of 1.6 was defined to differentiate between healthy males and obstructed patients. However, the equipment needed to perform the test is expensive and specialized, and a larger patient population study would be necessary to validate the method.

In the literature, high urinary flow velocities (up to 300cm/s) have been reported (18). According to the law of mass conservation,

$$Velocity\ (v) = Flow\ rate\ (Q)/Area\ (A)$$

A decrease in urethral cross-sectional area (A) due to BOO may result in even higher urinary flow velocities and could cause turbulence in the flow. At such high flow velocity, aliasing in the flow can limit the use of color Doppler ultrasound. In Doppler, Continues Wave (CW) and Pulsed Wave (PW) methods are used. Using CW Doppler, high velocities can be measured without aliasing but also no spatial (depth) information is available. In PW Doppler, spatial information can be acquired but at very high flow velocities and/or in the presence of turbulent flow, aliasing can occur and displayed as a bright turbulent color as shown in Figure 4.

1.6 Decorrelation Method

Instead of a frequency shift, the decorrelation method compares the scatter pattern of a group of images constructed from sequentially acquired ultrasound radiofrequency signals reflected by small scattering particles. If the particles move slowly, the images will be similar i.e. highly correlated, so there is not much decrease in correlation (decorrelation). If the particles move fast, then the correlation between images quickly decreases and there is a high decorrelation. Therefore the decorrelation dependency on the flow velocity is an obvious property and it may provide a possibility for estimating high urine flow velocities without aliasing (19). In cardiology, this method has been used to estimate the blood flow velocity in diseased arteries using intravascular ultrasound catheters (20, 21). Urethral obstruction may also lead to high urinary flow velocities and turbulent flow in the bulbar part of urethra. By placing the transducer gently at the perineum we can acquire ultrasound data of the urinary flow and estimate the decorrelation caused by obstruction of the urinary flow (see Figure 5). A high degree of obstruction causes more turbulence in the flow and leads to high decorrelation between sequential ultrasound radiofrequency signals.

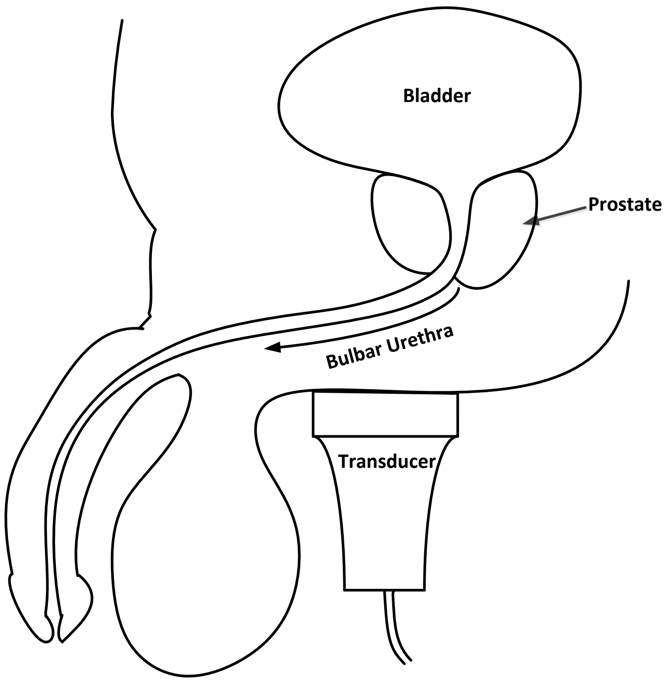

Figure 5: *Schematic drawing of the anatomy of the anatomical part of lower urinary tract.*

2. Outline of the thesis

2.1 Aim of the thesis: The aim of this thesis is developing a non-invasive, accurate and patient friendly method to diagnose BOO in patients with LUTS. To achieve this objective, we studied ultrasonic imaging of urinary flow velocity and turbulence caused by obstruction using radiofrequency ultrasound signals. We introduced the decorrelation technique in urology to measure high urinary flow velocity and to quantify turbulence due to obstruction. Our objective was to relate the urinary flow velocity and turbulence to the degree of obstruction.

2.2 Thesis Outline: Chapter 2 describes the relation of urinary flow velocity estimation from the decorrelation of radiofrequency ultrasound signals in soft tissue mimicking urethra models. The decorrelation was studied in the near field, focal zone and far field of the ultrasound beam. Chapter 3 describes the effect of scattering particle concentration on the decorrelation process. We studied the change in the decorrelation of ultrasound signals in urethra models using both water with scattering particles and stepwise diluted urine from healthy volunteers. In chapter 4 the relationship between decorrelation of sequential ultrasound signals and the degree of obstruction was studied in urethra models. In chapter 5, the applicability of an ultrasound decorrelation method for urinary flow imaging was studied in healthy male volunteers, to provide a basis for a non-invasive approach to diagnose bladder outlet obstruction. Statistical variance analysis showed a significant difference in ultrasound decorrelation slope between volunteers. Chapter 6 describes the application of the decorrelation method in BOO patients using the relations described in chapter 4 and chapter 5. Chapter 7 discusses the merits of the developed method and provides a future prospective and conclusion of the study.

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PART II

IN-VITRO STUDIES

Chapter 2

Estimation of urinary flow velocity in models of obstructed and unobstructed urethras by decorrelation of ultrasound radiofrequency signals.

Based on the publication:

Arif M, Idzenga T, van Mastrigt R, de Korte CL. Estimation of urinary flow velocity in models of obstructed and unobstructed urethras by decorrelation of ultrasound radiofrequency signals. Ultrasound Med Biol 2014;40:938-46.

Abstract

Aims: The feasibility of estimating urinary flow velocity from the decorrelation of radiofrequency (RF) signals was investigated in soft tissue-mimicking models of obstructed and unobstructed urethras.
Methods: The decorrelation was studied in the near field, focal zone and far field of the ultrasound beam. Furthermore, the effect of beam width was investigated.
Results: The results of this study suggest that it is feasible to estimate flow velocity in models of the urethra by quantifying the decorrelation of RF ultrasound signals. The decorrelation slope increased more rapidly and more linearly with increasing velocity in the focal zone than in the near and far field.
Conclusion: A preliminary example of an in vivo measurement in a healthy volunteer illustrated that this method has potential for clinical use in the future.

1. Introduction

Bladder outlet obstruction (BOO) is a common disease in elderly men often caused by benign prostatic enlargement (see Fig. 1). Lower urinary tract symptoms (LUTS) such as a weak urinary stream, dribbling and frequent voiding (also nocturnal) are mostly the result of BOO and have a significant negative impact on the patient's quality of life (1, 2). Another possible cause of the same symptoms is a weakly contracting bladder. Currently, a urodynamic pressure-flow study is the standard procedure for differential diagnosis of LUTS (3). In this diagnostic method, one double-lumen catheter is inserted into the urinary bladder via the urethra, and a single-lumen catheter is inserted into the rectum. One lumen of the bladder catheter and the lumen of the rectal catheter are connected with pressure transducers to measure intravesical pressure, p_{ves}, and abdominal pressure, p_{abd}, respectively, at maximum urinary flow rate, Q_{max}. The difference between p_{ves} and p_{abd} is called the detrusor pressure, p_{det}, which is the pressure caused by contraction of the bladder (detrusor). The other lumen of the bladder catheter is used to fill the bladder with a saline solution. On the basis of these data, the patient is diagnosed as obstructed, unobstructed or equivocal using a pressure-flow nomogram (3). The degree of obstruction is quantified using the Bladder Outlet Obstruction Index (BOOI) (3), calculated as

$$BOOI = p_{det} - 2.Q_{max} \tag{1}$$

The invasive nature of the standard diagnostic method makes it patient unfriendly and may cause pain and acute urinary tract infections. A variety of non-invasive and more patient-friendly methods have been proposed to diagnose BOO in patients with LUTS, such as the condom-catheter method (4), the cuff method (5), perineal sound recording (6) and Doppler flowmetry (7). However, as yet, these methods cannot adequately replace the standard invasive diagnostic method.

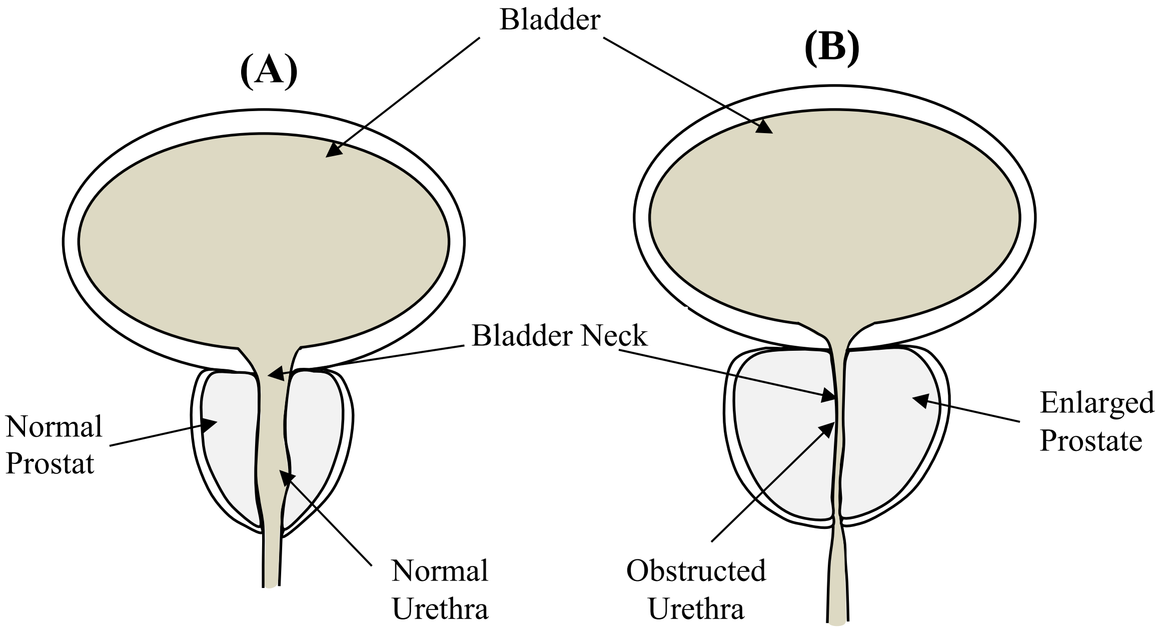

Figure 1: *Drawings of the cross-section of (A) a normal prostate and (B) an enlarged prostate causing bladder outlet obstruction.*

It was thought that urine does not contain particles that scatter ultrasound signals (8, 9). However, Elliot and Rabinowitz (10) and Verdesca et al. (11) identified different types of crystals in urine. Crystalline structures such as calcium oxalate, uric acid and amorphous urates were the most frequent (11). Calcium oxalate crystals occur in urine in the dihydrate and monohydrate format and account for 76% of all crystals. The monohydrate crystals range from 2 to 34 mm; the dihydrate crystals range from 2 to 104 mm (10). Furthermore, Kumon et al. (9) reported that based on Bernoulli's principle, a decrease in pressure can occur in the urethra. This pressure decrease is caused by accelerated urine flow from the bladder into the urethra and may lead to the creation of microbubbles as a result of cavitation.

In the literature, the urine velocity at the bladder outlet is reported to be on the order of 100 cm/s and may be as high as 300 cm/s in young boys (12, 13). When the urethra is obstructed, velocities are even higher. Ozawa et al. (7) used color Doppler ultrasound to diagnose BOO by measuring the ratio of flow velocity values at two different positions, downstream and in the obstruction. However, the effect of aliasing at higher flow velocities limits the use of color Doppler ultrasonography in measurement of urine flow velocity. A time-domain correlation method may provide an advantage in estimating these higher urine flow velocities without aliasing (14). This method has been used to estimate blood flow velocity in arteries using intravascular ultrasound catheters (15-17). The basic principle underlying this correlation method is that when a group of randomly distributed scattering particles move across an ultrasound beam, the correlation between received signals decreases (decorrelates) as a function of time. The rate of decorrelation between subsequent radiofrequency (RF) signals is a function of the flow velocity, pulse repetition interval (PRI) and beam characteristics of the transducer (16, 18).

In fluid dynamics, according to the law of mass conservation ($Av = Q$), at a specific flow rate and constant cross-sectional area (A) along the tube, flow velocity remains constant. However, in the case of an obstruction in the tube and at a constant flow rate, the cross-sectional area in the obstruction is decreased, which results in increased flow velocity and a higher decorrelation rate in that region. Therefore, we performed an experimental study to estimate flow velocity from the decorrelation information in models of obstructed and unobstructed urethras. In addition, measurements were made in volunteers to determine if the urinary stream could be imaged by time-domain correlation of RF signals during voiding.

2. Materials and Methods

2.1 Model Experiments

2.1.1 *Polyvinyl alcohol urethra model*: Polyvinyl alcohol (PVA) cryogel was used to make a soft tissue-mimicking phantom representing the male lower urinary tract (19). A 10% aqueous solution of PVAwas heated in water for 30 min and poured into a cylindrical mold (450 mm in length, 16 mm in crosssectional diameter). A circular copper wire (5 mm in cross-sectional diameter) was placed along the center of the mold to create a flow channel through the urethra model. The mold was kept at room temperature (24^{o}C) for the first 6 h. Some free space was maintained at the top of the mold to remove air bubbles from the solution and, thus, allow the urethra model to have a uniform composition. Subsequently, the mold was stored in a freezer at –20^{o}C for 14 h and again at room temperature for 10 h. This procedure constitutes one freeze-thaw cycle, and the PVA model urethra was subject to two such freeze-thaw cycles (20). The number of freeze-thaw cycles controls the elasticity of the model. To create an obstruction in the urethra model, a flexible PVA ring (with internal and external diameters of 7 and 29 mm, respectively) was placed around the urethra (see Fig. 2 A). The PVA ring was also subjected to two freeze-thaw cycles.

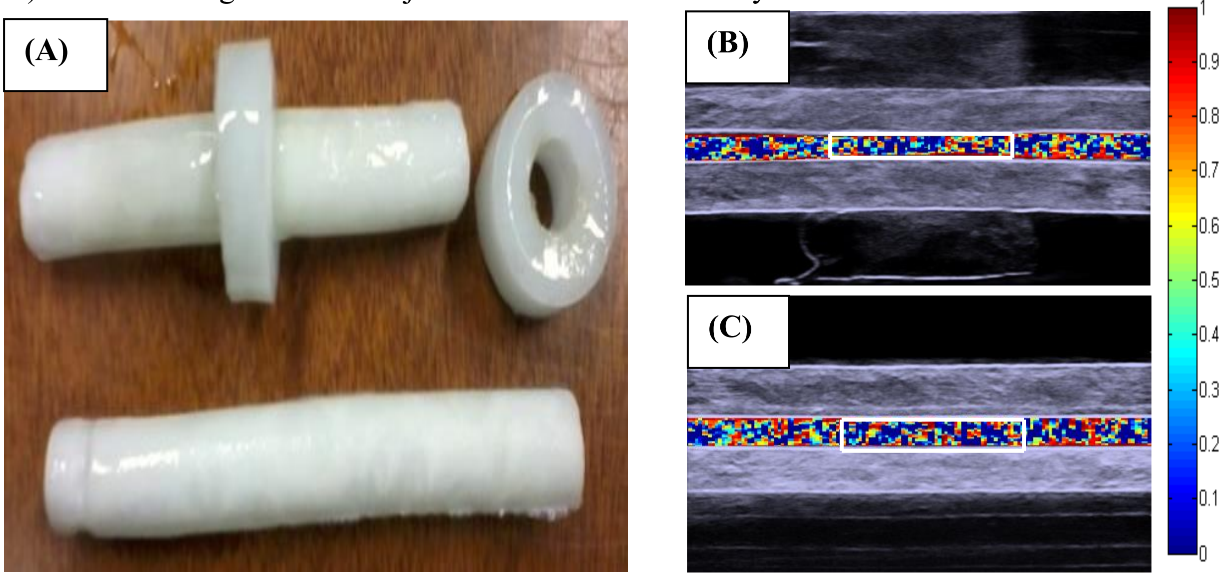

Figure 2: *(A) Flexible polyvinyl alcohol ring and model urethra mimicking the lower urinary tract of a male. Correlation images for (B) obstructed (C) unobstructed urethra models at a flow rate of 6 mL/s.*

2.1.2 *Measurement setup*: The model urethra was placed in a water-filled container to prevent evaporation. The water also acted as an ultrasound coupling medium (see Fig. 3). To generate flow through the urethra model, one end was connected to a water column representing bladder pressure. The other end was connected to an outflow tube draining into a fluid-filled expansion barrel through a rotating disk uroflowmeter (Disa Electronic, Taastrup, Denmark). The fluid from the barrel was pumped back into the water column through a roller pump (SF-240, Verder, Utrecht, The Netherlands). Two grams of silica gel particles (Sigma-Aldrich, St. Louis, MO, USA) 15–40 μm in size was added to 1 liter (L) of water to mimic the ultrasound-reflecting particles in urine.

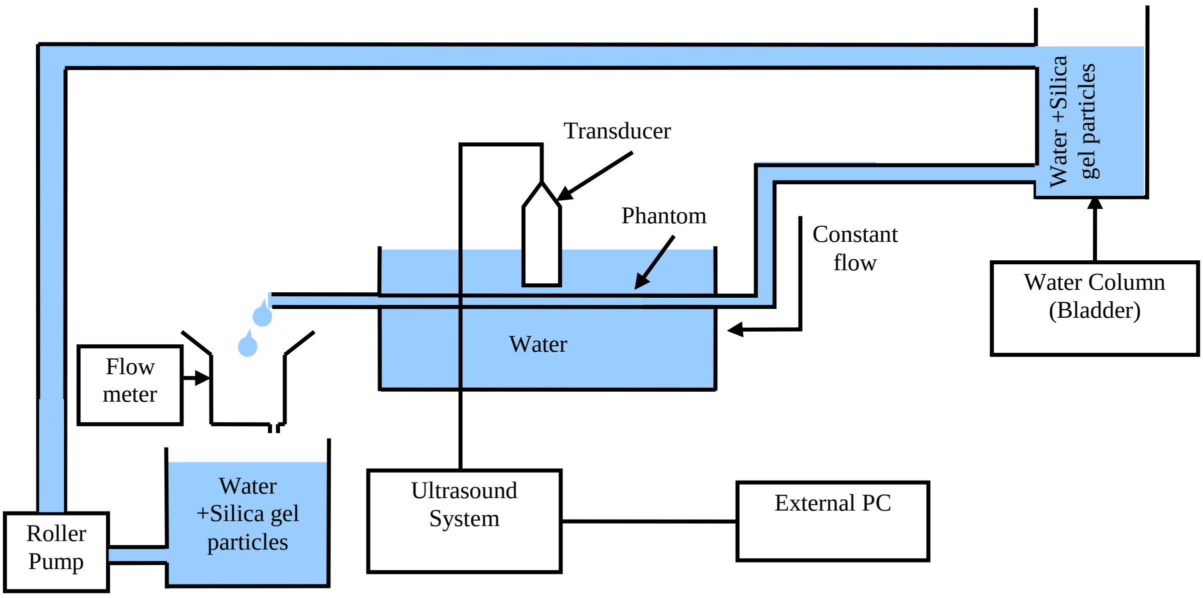

Figure 3: *Experimental setup.*

2.1.3 *Data acquisition*: An ultrasound system (Pro Focus UltraView 2202, BK Medical, Herlev, Denmark) with a custom-designed RF interface was used to acquire RF data. The ultrasound system was equipped with a 5-MHz linear array transducer (8670), consisting of 128 transducer elements with a pitch of 0.3 mm. For flow measurement, a pulse transmission mode was used. Ten subsequent RF signals were transmitted and received 14 times at a pulse repetition frequency (PRF) of 9 kHz. Each RF signal yielded a single A-line in the image. From the 1st transmission, the 1st RF signal gives the first A-line in image 1, the 2nd RF signal gives the 1st A-line in image 2 and the 10th RF signal yields the 1st A-line in image 10. From the 2nd transmission, the 1st RF signal gives the 2nd line in image 1, the 2nd RF signal gives the 2nd A-line in image 2 and the 10th RF signal gives the 2nd line in image 10. We repeated this process 144 times and acquired 10 images (RF data sets) each composed of 144 adjacent ensembles of 10 RF signals. To investigate the influence of the beam profile on the decorrelation rate, the probe was positioned parallel to the flow direction. The experiment was performed at three different axial beam positions: near field, focal zone and far field. This was achieved by changing the position of the models with respect to the transducer. The received RF signals were stored on an external PC using a frame grabber (OR-X4 C0-SE-F00, Imago Group, Waalre, The Netherlands). The RF data were acquired at a sampling frequency (f_S) of 20 MHz.

2.1.4 *Data processing/analysis*: The RF data were processed using MATLAB (The MathWorks, Natick, MA, USA). A temporal correlation method was applied to evaluate the changes in 144 adjacent ensembles of 10 RF signals (17). In this method, the correlation coefficients between the first and nine consequential RF data sets (1 with 2, 1 with 3, 1 with 4, etc.) were calculated to construct correlation images. The correlation coefficients, $\rho_{i,j}$, between two RF signals, $S_i(n)$ and $S_j(n)$, were calculated as

$$\rho_{i,j} = \frac{\sum_{n=1}^{N}\left[\left(S_i(n) - \overline{S_i}\right)\left(S_j(n) - \overline{S_j}\right)\right]}{\sqrt{\sum_{n=1}^{N}\left(S_i(n) - \overline{S_i}\right)^2 \sum_{n=1}^{N}\left(S_j(n) - \overline{S_j}\right)^2}} \quad (2)$$

where $i = 1$; $j =$ number of RF signals (10); $N =$ number of adjacent ensembles (144) of 10 RF signals; and $\bar{S} =$ mean value of signal. In 10 correlation images constructed from 144 adjacent ensembles of 10 RF signals, a region of interest (ROI) was selected. As the correlation coefficients were not normally distributed in the ROI, we applied the Fisher Z-transform (21):

$$z = \frac{ln(1+\rho) - ln(1-\rho)}{2} \quad (3)$$

After Fisher Z-transformation, we calculated the average of all pixels in the ROI, called the mean $\bar{z}$ and transformed it back to the time domain by computing the inverse Fisher Z-transformation to obtain the mean correlation coefficients:

$$\overline{\rho} = \frac{e^{2\bar{z}} - 1}{e^{2\bar{z}} + 1} \quad (4)$$

The decorrelation curve was obtained by plotting these mean correlation coefficient values as a function of the interval between two correlated RF signals (0.11 ms).

2.1.5 *Decorrelation–flow velocity relationship*: The decorrelation curves at different values of flow velocity (ranging from 0 to 300 cm/s) were plotted for both obstructed and unobstructed urethra models. The flow velocities were calculated from the cross-sectional area (A) measured using ultrasound at the ROI for different flow rates (3–18 mL/s). The flow rates were measured with a rotating disk uroflowmeter. For each decorrelation curve, the decrease in correlation value at an interval of 0.11 ms (interval between two subsequent RF signals) was calculated and plotted as a function of flow velocity. To increase the accuracy of the correlation estimate, we calculated the correlation coefficients between each two 144 adjacent ensembles of 10 RF signals (1 with 2, 2 with 3, 3 with 4, etc.) and took the mean value, ρ_{mean}.

To determine the relationship between decorrelation rate and flow velocity, we calculated the decorrelation slope and plotted this as a function of flow velocity. The decorrelation slope, of each decorrelation curve (16) at different values of flow velocity was calculated as

$$\overline{\rho} = \frac{e^{2\bar{z}} - 1}{e^{2\bar{z}} + 1} \tag{5}$$

where $\Delta t =$ interval between two subsequent RF signals (0.11 ms).

2.1.6 *Ultrasound beam width*: In optics, the f-number is the ratio of the focal length of the lens to the diameter of the entrance pupil. In ultrasound systems, by varying the f-number, one can change beam width, which affects ultrasound beam focusing and the decorrelation rate. To study this effect, we calculated the decorrelation slope in the model of an obstructed urethra by varying the ultrasound beam width at the focal zone.

2.2 In vivo experiment

We acquired ultrasound data from a healthy volunteer to verify that the urine contains particles that scatter ultrasound signals and that these scatter signals can be used for our decorrelation method. The data acquisition and analysis process was similar to that described for the phantom study. A linear array transducer (8670, BK Medical) was used to acquire ultrasound RF signals at a PRF of 12 kHz. The PRF value is related to image depth. At a higher image depth, the PRF should be lower. In the phantom study, we positioned our urethra models at three different axial beam positions requiring increased image depth and, thus, lower PRF values than in the in vivo experiment. In the healthy volunteer, a trans-perineal ultrasound probe holder was used to achieve gentle contact between the transducer and the perineal skin. The volunteer voided in the standing position. The urinary flow rate was measured using a rotating disk uroflowmeter (Disa Electronic). The focal zone of the ultrasound beam was positioned at the urethra. The ultrasound beam width was wider (f-number = 5.5) than in the phantom study. The participant had given his informed consent, and the research was carried out in accordance with the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

3. Results

3.1 Model Experiments

3.1.1 *Decorrelation–flow velocity relationship*: Examples of correlation images constructed between the 1st and 10th RF data sets of the obstructed and the unobstructed urethra models superimposed on separately collected Bmode images at flow velocities of 75 and 100 cm/s are provided in Figure 2(B, C). Decorrelation curves at three different axial beam positions: near field, focal zone and far field are provided in Figures 4, 5 and 6, respectively. A wide range of flow velocity values (0–300 cm/s), especially higher velocities, were tested to check the validity of our method. We observed that the higher the velocity, the more rapid was the decay of correlation. For each decorrelation curve, the decrease in correlation after 0.11 ms is illustrated in Figure 7(A) for models of both obstructed and unobstructed urethras. The experiments were done three times, and the error bars in Figure 7(A) represent the associated standard deviations. The decorrelation slope is plotted as a function of calculated velocity for both models in Figure 7(B). The decorrelation slope increases slowly with increasing velocity in the near and far field for both types of models and increases more rapidly and more linearly in the focal zone.

3.1.2 *Ultrasound beam width*: The model of an obstructed urethra was positioned at the focal zone of the ultrasound transducer.We calculated the decorrelation slope with the increase in flow velocity at three different f-numbers (or beam width): 5.5, 3 and 1 (see Fig. 8). At smaller beam widths, the decorrelation slope increased more rapidly.

3.2 In vivo experiment

Figure 9(A) is the anatomic B-mode image of the bladder and urethra of the healthy volunteer. The correlation images were constructed between the 1st and nine RF data sets acquired during urinary flow in the male volunteer. The correlation image constructed between the 1st and 10th RF data sets is superimposed on the selected region in the separately collected B-mode image of the male urethra in Figure 9(B). The correlation image of urinary flow confirms that urine contains particles that scatter ultrasound signals and that these scatter signals can be used in our decorrelation method.

4. Discussion

In this study, a decorrelation method was tested to estimate urinary flow velocity in models of obstructed and unobstructed urethras. The decorrelation method provides an advantage over pulsed wave Doppler ultrasound in that it can be used to estimate higher flow velocities without aliasing. In the model of an unobstructed urethra, at a constant flow rate, the cross-sectional area along the model, and hence the flow velocity, remained constant. However, in the model of an obstructed urethra, the cross-sectional area of the obstructed region decreased, resulting in a higher velocity and, thus, greater displacement of particles during the same time interval and a higher decorrelation rate. In Figure 4, we see that at the same flow rate (i.e., Q = 6 mL/s, v = 75 cm/s [unobstructed], v = 100 cm/s [obstructed]), the decorrelation rate in the obstructed urethra model is higher than that in the unobstructed urethra model.

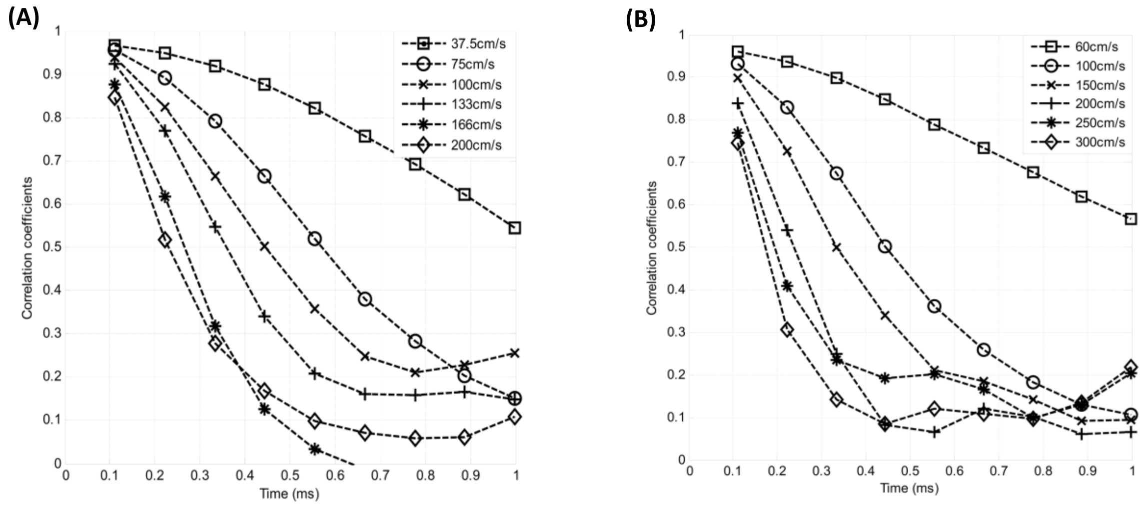

Figure 4: *Decorrelation curves as a function of time interval at different flow velocity values for (A) unobstructed and (B) obstructed urethral models in the near field.*

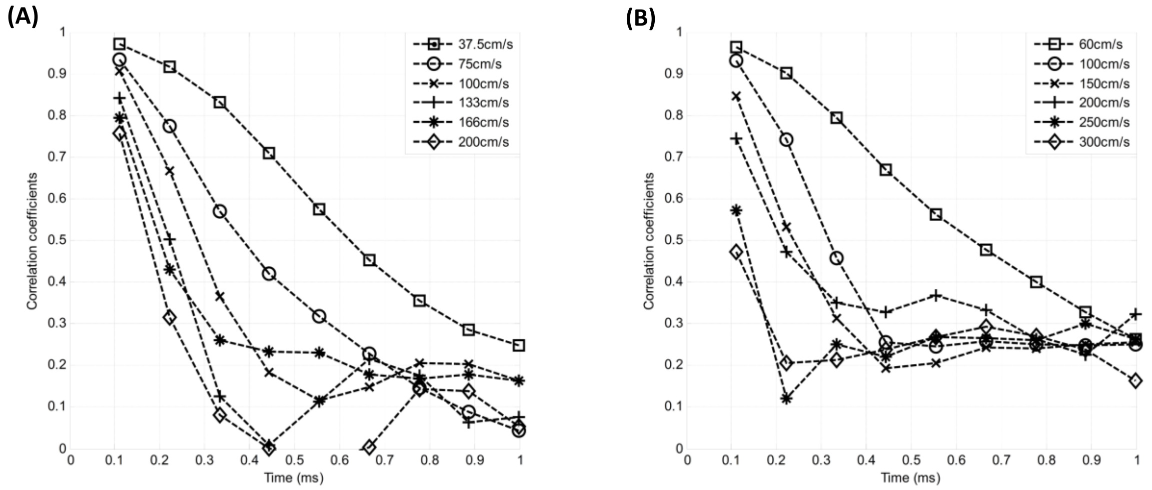

Figure 5: *Decorrelation curves as a function of time interval at different flow velocity vlaues for (A) unobstructed and (B) obstructed urethral models in the focal zone.*

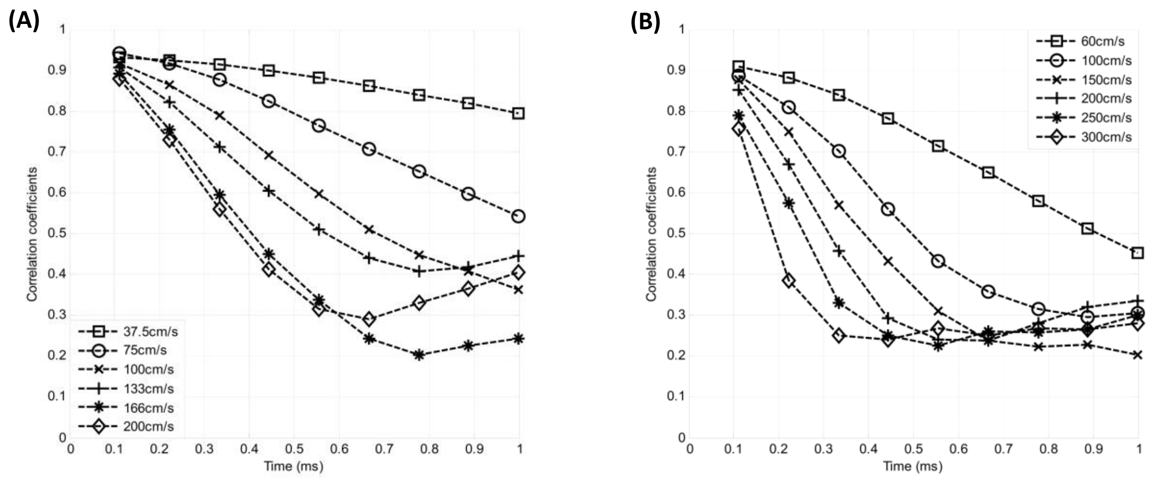

Figure 6: *Decorrelation curves as a function of time interval at different flow velocity vlaues for (A) unobstructed and (B) obstructed urethral models in the far field.*

Analysis of decorrelation rate revealed that the decay pattern of the decorrelation curve is highly dependent on the beam characteristics of the transducer. The beam profile of an ultrasound transducer can be divided into three zones: near field, focal zone and far field. The near field is the region between the transducer surface and the focal zone, and the far field is the region posterior to the focal zone. The beam width is narrow in the focal zone compared with the near and far field. In our experiments, the urethra models were placed at all three different beam profile positions. As velocity increased, the decorrelation rate was slow in the near and far field and faster and more linear in the focal zone (see Fig. 7A). The faster decorrelation rate in the focal zone is due to the smaller beam width. Consequently, the particles move faster in and out of the region with sufficient ultrasound intensity compared with the particles in the near and far field. For a wider focal zone, the correlation between subsequent signals is higher, and consequently, the decorrelation rate is slower. Therefore, to calibrate the decorrelation properties and to find a suitable relationship to estimate flow velocity from the decorrelation, we narrowed the focus region by decreasing the f-number (or beam width) from 5.5 to 1. Similar decorrelation profiles were found for f-numbers of 3 and 5, whereas an f-number of 1 resulted in more rapid decorrelation. Changing the beam width affects the decorrelation rate, and proper selection of the beam width allows adjustment of the velocity range that can be measured. Taking the average of correlation coefficient values measured with a number of two subsequent signals (between 1 and 2, 2 and 3, 3 and 4, etc.) at different flow velocities increases the accuracy of decorrelation rate measurement.

Li et al. (16) found that the decorrelation slope is suitable for quantifying the decorrelation process and provided the basis for deriving flow velocity from decorrelation. In their study in a plastic arterial phantom, the decorrelation slope increased almost linearly with flow velocity for a low flow velocity range (0–50 cm/s). In our study in models of the urethra, we also found a linear relationship between decorrelation slope and flow velocity up to 300 cm/s in the focal zone. This can be explained by the use of a relatively low central frequency and consequently wider focal zone in our study with respect to their study (30 MHz). We also found that the same linear relationship can be used to estimate urinary flow velocity in both obstructed and unobstructed urethra models (see Fig. 7B). To estimate very high flow velocities (e.g., ≥ 800 cm/s), the beam width needs to be adjusted or measurements have to be performed in the far field, which is characterized by a slower decorrelation rate.

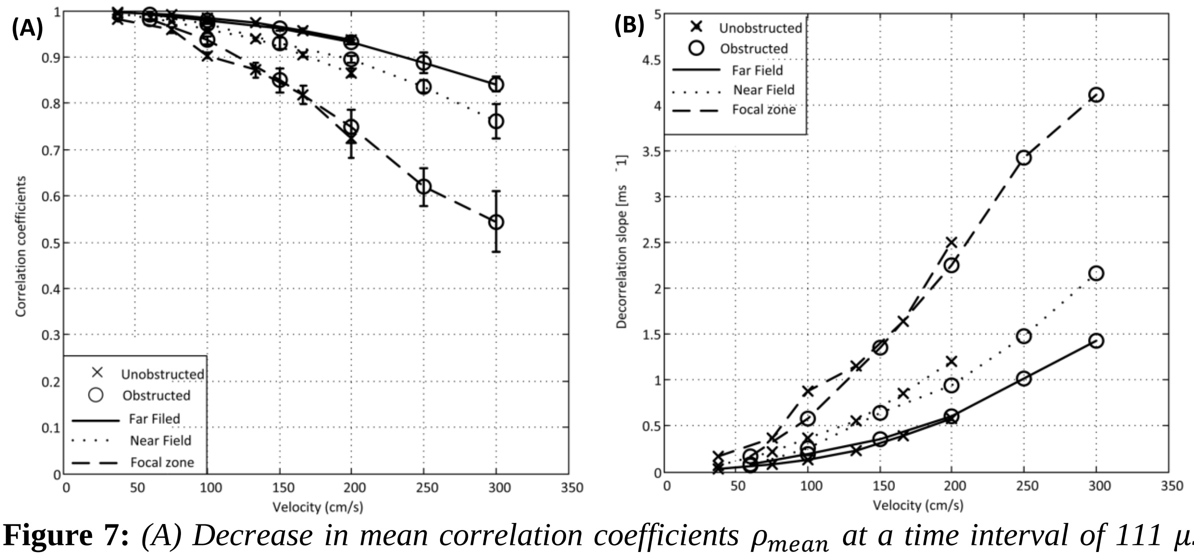

Figure 7: *(A) Decrease in mean correlation coefficients ρ_{mean} at a time interval of 111 µs with flow velocities in unobstructed (x) and obstructed (o) urethra models. (B) Measured decorrelation slope and flow velocity for models of unobstructed and obstructed urethras.*

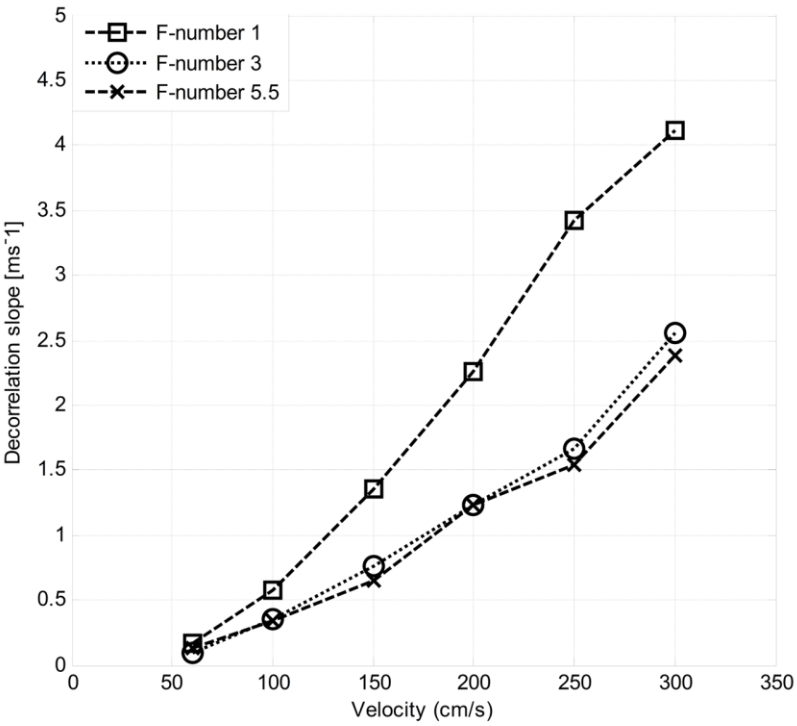

Figure 8: *Decrease in mean correlation coefficients with flow velocity in urethral models with different f-numbers.*

The decorrelation rate at a certain flow velocity is determined mainly by the beam characteristics of the ultrasound transducer, which differ among the different ultrasound systems. Also, the decorrelation rate is position dependent; therefore, to accurately estimate flow velocity, the decorrelation rate should be measured as a function of axial beam position for the complete scan depth. The correlation image constructed from the RF ultrasound signals acquired from the urethra of a healthy volunteer during voiding supports the hypothesis that urinary flow can be estimated in humans by using a correlation method based on RF ultrasound signals.

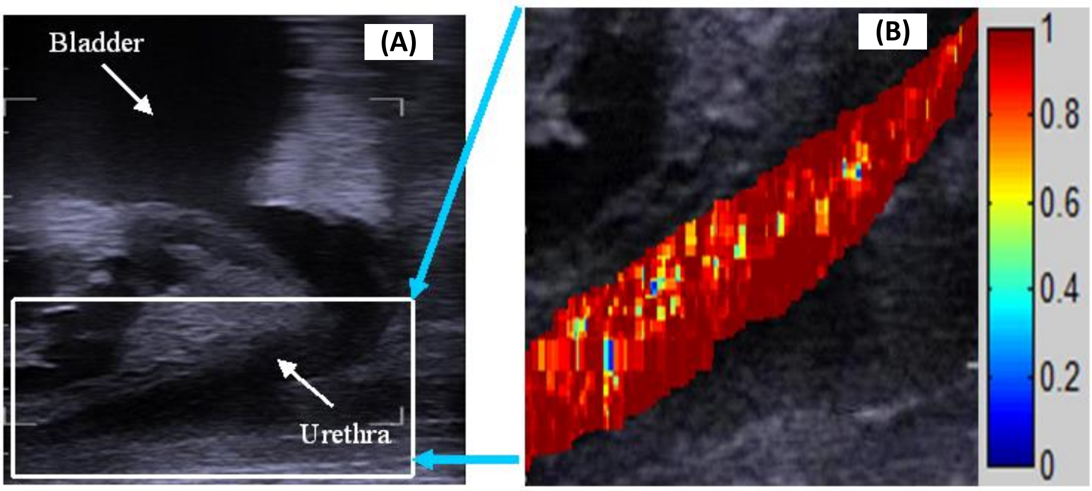

Figure 9: *(A) B-mode image of male urethra. (B) A correlation image superimposed on a part of a B-mode image of a male urethra.*

The traditional color Doppler technique and decorrelation method both use pulse transmission mode. A sequence of pulses are fired, and the signals from the scattering medium are received. If the scattering medium does not change, the received signals are identical. If the scattering medium is moving, the received signals are different. Both methods use this difference to derive the velocity of the medium. Both techniques are angle dependent. The decorrelation method works best at a 90^o angle between the flow and the ultrasound beam to receive maximum scattered signals, whereas Doppler works best at a 0^o angle for accurate flow velocity estimation. The decorrelation method is also a more time- and computation-demanding technique compared with the Doppler method. A problem with data acquisition of fast-moving particles over a longer distance and longer acquisition time is that the local density of the scatterers changes with flow. This change is small for a high acquisition rate; however, if the interval between acquisitions lengthens, the change in speckle pattern becomes large and may affect the results.

5. Conclusion

The decorrelation of subsequently acquired ultrasound RF signals can provide a basis for flow velocity estimation. We suggest a new application of this method to estimate urinary flow velocity in models of the urethra. Results of this study indicate that it is feasible to estimate flow velocities in a wide range (0–300 cm/s) in models of obstructed and unobstructed urethras from the decorrelation of RF ultrasound signals. Because of the smaller beam width in the focal zone, the decorrelation slope increases more rapidly and more linearly than there than in the near and far field. A preliminary measurement in a healthy volunteer revealed the potential of this method as a future non-invasive method for clinical estimation of urinary flow velocity.

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Chapter 3

Dependence of ultrasound decorrelation on urine scatter particle concentration for a non-invasive diagnosis of bladder outlet obstruction

Based on the publications:

Arif M, Idzenga T, de Korte CL, van Mastrigt R. Dependence of ultrasound decorrelation on urine scatter particle concentration for a non-invasive diagnosis of bladder outlet obstruction. Neurourology & Urodynamics 34(8), p 781 – 6, 2015.;

Arif M, Idzenga T, van Mastrigt R, de Korte CL. Dependence of ultrasound decorrelation on urine scatter particle concentration. Proc. Ultrasonics Symposium (IUS) IEEE International 2014, 1873-1875.

Abstract

Aims: To develop a non-invasive method to diagnose Bladder Outlet Obstruction (BOO) based on decorrelation of subsequently acquired UltraSound (US) data of urinary flow, we studied the influence of scatter particle concentration on the decorrelation process in urethra models using both aqueous solutions of scattering particles and urine samples.
Methods: A tissue mimicking urethra model made from PolyVinyl Alcohol (PVA) solution was infused with seven aqueous solutions containing different particle concentrations at a constant flow rate value of 10 ml/sec. The average correlation coefficients between subsequentUSimages were calculated and plotted as a function of particle concentration. This procedure was also applied to stepwise diluted urine samples from nine healthy volunteers. An inversely exponential curve was fitted to the experimental data to estimate the scatter particle concentration in the urine samples.
Results: The average correlation values between subsequent US images increased with the particle concentration. The morning urine samples contained an appropriate number of scattering particles to make clinical application of the decorrelation method possible. The fitted correlation curves made an estimation of urine particle concentration possible.
Conclusion: The results of this study show that morning urine is suitable for US decorrelation without correcting for differences in particle concentration

1. Introduction

In urology, color Doppler Ultrasound has been used for urinary flow imaging. In 2010, Ozawa et al. (1) published that the ratio of urinary flow velocity values measured by Doppler US at two different positions (i.e., downstream of obstruction and in the obstruction) could be used to non-invasively diagnose Bladder Outlet Obstruction (BOO). However, high urinary velocity values in the urethra have been reported in the literature. Velocities at the bladder outlet were in the order of 100 cm/sec and maybe up to 300 cm/sec in young boys (2, 3). Obstruction of the urethra may lead to even higher velocities. Such high velocities may cause an aliasing effect and thereby limit the use of color Doppler ultrasonography. In IntraVascular Ultra Sound (IVUS), assessment of blood flow velocity by a time-domain correlation-based method has been used to evaluate the functional status of diseased (stenosis) arteries. We have shown that this correlation method could also be used to estimate high flow velocities in obstructed and unobstructed urethras without aliasing (4). The basic principle of this method is that it compares the scatter pattern of particles in a group of subsequent US images. If the particles move slowly and the flow is laminar the images will be similar and highly correlated. However, if the particles move fast or flow is not laminar anymore, there will be more difference in scatter patterns between subsequent images and the correlation between images will be lower, which is also known as decorrelation.

A question that remains however is whether urine is suitable for estimating this decorrelation of US signals. Ozawa et al. (1) have demonstrated that the US signals originating from urine are sufficient to generate a detectable Doppler shift. They postulated that the US signals might be scattered by microbubbles, generated as a result of cavitation. On the other hand different types of crystals have been identified in urine that could function as scattering particles (5, 6). Calcium oxalate, uric acid, and amorphous urates are the most frequent crystalline structures (6). Dihydrate and monohydrate types of calcium oxalate crystals account for 76% of all crystals. The monohydrate crystals range from 2 mm to 34mm and the dihydrate crystals from 2 mm to 104mm (5). These crystals also have the potential to act as scattering particles. However, the concentration of these crystals in urine is not known. Also between and within patients the concentrations may vary. Furthermore, the particle concentrations may have an effect on estimating the decorrelation of US signals. Therefore, we studied the influence of particle concentration on the decorrelation of US signals in urethra models using both water with scattering particles and stepwise diluted urine from nine healthy volunteers.

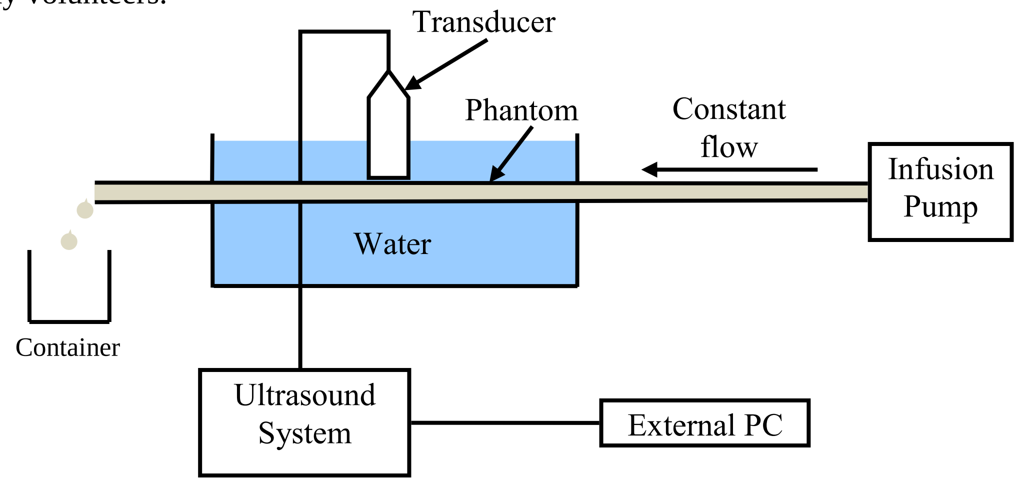

Figure 1: *Schematic drawing of the experimental setup.*

2. Materials and Methods

2.1 Urethtra Model

A soft tissue mimicking urethra model representing part of the lower urinary tract of a male was made from a 10% aqueous solution of PolyVinyl Alcohol (PVA) (7). PVA solution was heated in water for 30 min and poured in a cylindrical mould (450mm in length and 16mm in cross-sectional diameter). To create a flow channel through the model a circular copper wire (5mm in cross-sectional diameter) was placed along the central axis of the mould. The mould was first kept at room temperature (24^{o}C) and some free space at the top of the mould was left to allow air bubbles to escape from the solution. After 6 hr of rest, the mould was stored in a freezer at -20^{o}C. After 14 hr in the freezer the mould was kept at room temperature again for 10 hr. This procedure constituted one freeze-thaw cycle. The urethra model was freeze-thawed 2-times. The stiffness of the model increased with the number of freeze-thaw cycles (7).

2.2 Experiments

For the US data collection we placed the urethra model in a water filled container (see Fig. 1). The water acted as an US coupling medium and also prevented dehydration of the phantom. An infusion pump (2202, Harvard Apparatus, USA) was used to generate flow of different solutions through the model at a fixed flow rate of 10ml/sec. Silica gel particles of size 15–40µm (Sigma-Aldrich, St. Louis, MI) were added to water to mimic US reflecting particles in urine. We prepared seven of these aqueous solutions with increasing concentrations of scattering particles (i.e., 0.24mg/L, 0.47mg/L, 0.94mg/L, 1.86mg/L, 3.75mg/L, 7.50mg/L, 15mg/L). Furthermore, morning urine samples (we called this 100% dilution) from nine healthy volunteers were collected and diluted with degassed tap water to prepare urine solutions with different concentrations (50%, 25%, 12.5%, 6.25%). The tap waterwas kept for 24 hr at room temperate to allow air bubbles to dissolve before using it to prepare aqueous solutions and diluted urine samples.

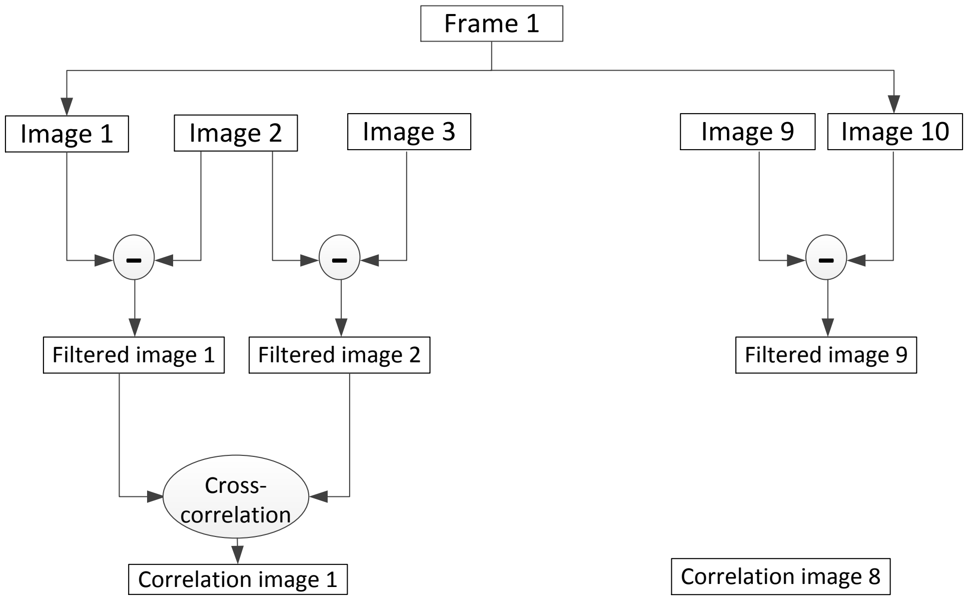

Figure 2: *A block diagram describing the principle of stationary echo cancellation and the data analysis.*

In each flow measurement, an US system (BK-Medical, Pro Focus UltraView 2202) equipped with a 5MHz linear array transducer (8670), was used to acquire 5 US frames (datasets). Each frame consisted of 10 subsequent US images acquired during flow of different solutions through the model at a time interval of 0.2 msec. The flow direction was in the transmitted US plane with the US beam perpendicular to the flow. The US data were stored on an external PC and processed using Matlab (The MathWorks, Natick, MA). The received US images from the phantom contained both stationary and flow related signal components. A filtering process was applied to the stored US images to cancel out stationary echoes from the phantom walls (See Fig. 2). By subtraction of subsequent images the stationary signals were canceled out but the signals related to particle motion remained (8-10).

After filtering, a correlation method was applied to evaluate the changes in the resulting nine subsequent US images (11) .In this method the correlation coefficients between two subsequent images (i.e., 1 with 2, 2 with 3, 3 with 4 etc.) were calculated to construct eight correlation images. To realize a normal distribution of the correlation coefficients, the Fisher Z-transformation was applied (a detailed explanation of the method can be found in Appendix A). In each correlation image a Region Of Interest (ROI) was selected and the mean correlation coefficient value was calculated. To increase the accuracy of the correlation estimate we calculated the average of these eight mean correlation values.

A nonlinear least squares method was used to fit the following equation:

$$Corr = a\,(1 - \exp(-bx)) + c \qquad (1)$$

to the dependence of the average correlation on the concentration of particles. Where Corr = average correlation value, x = particle concentration in mg/L. Assuming that at the same correlation value, the concentration of particles in aqueous solutions and the urine samples were equal, the coefficients a, b and c were used to calculate the concentration of particles in urine from each average correlation value for each volunteer as:

$$x = \frac{\ln\left(1 - \frac{Corr - c}{a}\right)}{-b} \quad , \qquad for\ Corr < a \qquad (2)$$

The calculated urine particle concentrations [x(mg/L)] for each urine solution were divided by the corresponding urine dilution percentage to calculate the conversion factor, used for the transformation of urine dilution percentage (%) to particle concentration (mg/L).

$$conversion\ factor\ (cf) = \frac{x(mg/liter)}{urine\ concentration(\%)} \qquad (3)$$

We took the mean of the conversion factors ($\overline{cf}$) for each volunteer and multiplied these with the urine dilution percentages to calculate urine particle concentrations for each urine solution in each volunteer. Using these calculated urine particle concentrations the correlation values were plotted.

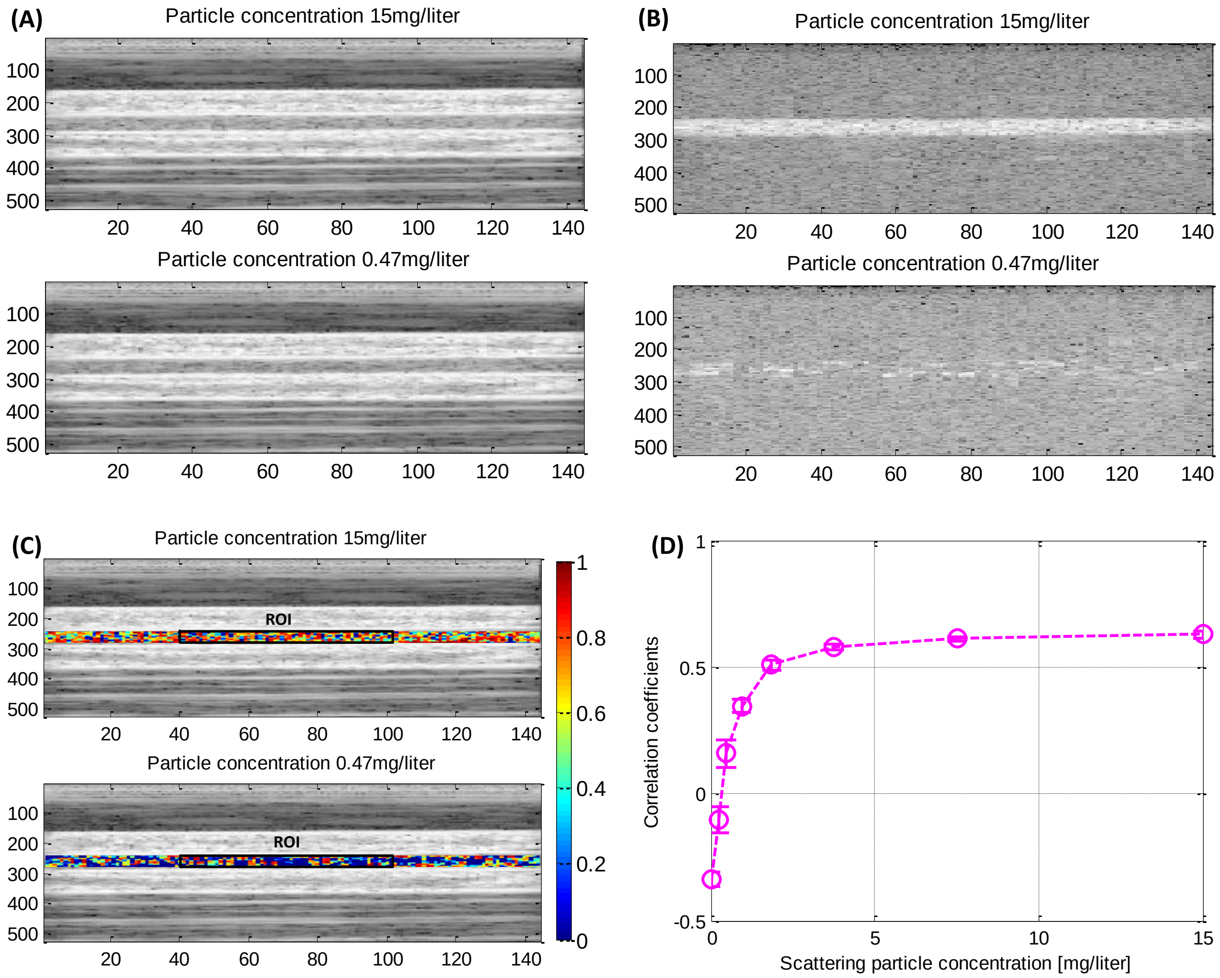

Figure 3: *Ultrasound images of the urethra model perfused with 15 mg/L (top) and 0.47 mg/L (bottom) aqueous solutions at a flow rate of 10ml/s (A) Before stationary echo cancellation. (B) After stationary echo cancellation. (C) Color coded correlation coefficients of flow through the urethra model perfused with 15 mg/L(top) and 0.47 mg/L (bottom) aqueous solutions at a flow rate of 10ml/s superimposed on ultrasound images. (ROI represents Region of Interest). (D) The average correlation values plotted as a function of the scattering particle concentration. The errorbars shows average ±1 standard deviation in five frames.*

3. Results

Examples of US images of perfusing the model with two aqueous solutions (15 mg/L and 0.47 mg/L) are presented in Figure 3(A). After filtering out the stationary signals, the resulting US images are shown in Figure 3(B). Most of the signals from the phantom wall were cancelled out and the flow signals were enhanced. Figure 3(C) illustrates the correlation images for both aqueous solutions superimposed on US images. It can be observed that for the high particle concentration (15 mg/L) the correlation coefficients are close to one and that they are smaller for the low particle concentration (0.47mg/L). The change in correlation with the concentration of particles is shown in Figure 3(D). The results show that the correlation increases inverse exponentially with the concentration of particles. The R-square value (0.9927) of the fitted curve demonstrates that the correlation is strongly related to the particle concentration.

The US images for two urine dilutions (100% and 12.50%) before and after filtering are shown in Figure 4(A) & (B). The correlation images superimposed on US images are shown in Figure 4(C). The correlation curves obtained from urinary flow show similar results to those of perfusion with tap water with added scattering particles (see Fig. 4(D)). Figure 5 shows the average correlation as a function of the scattering particle concentrations (mg/L) for the aqueous solutions and volunteer urine samples. The scattering particle concentrations in the urine samples were derived according to equations 2–3 using constants a (0.9433), b (1.403), and c (-0.3402).

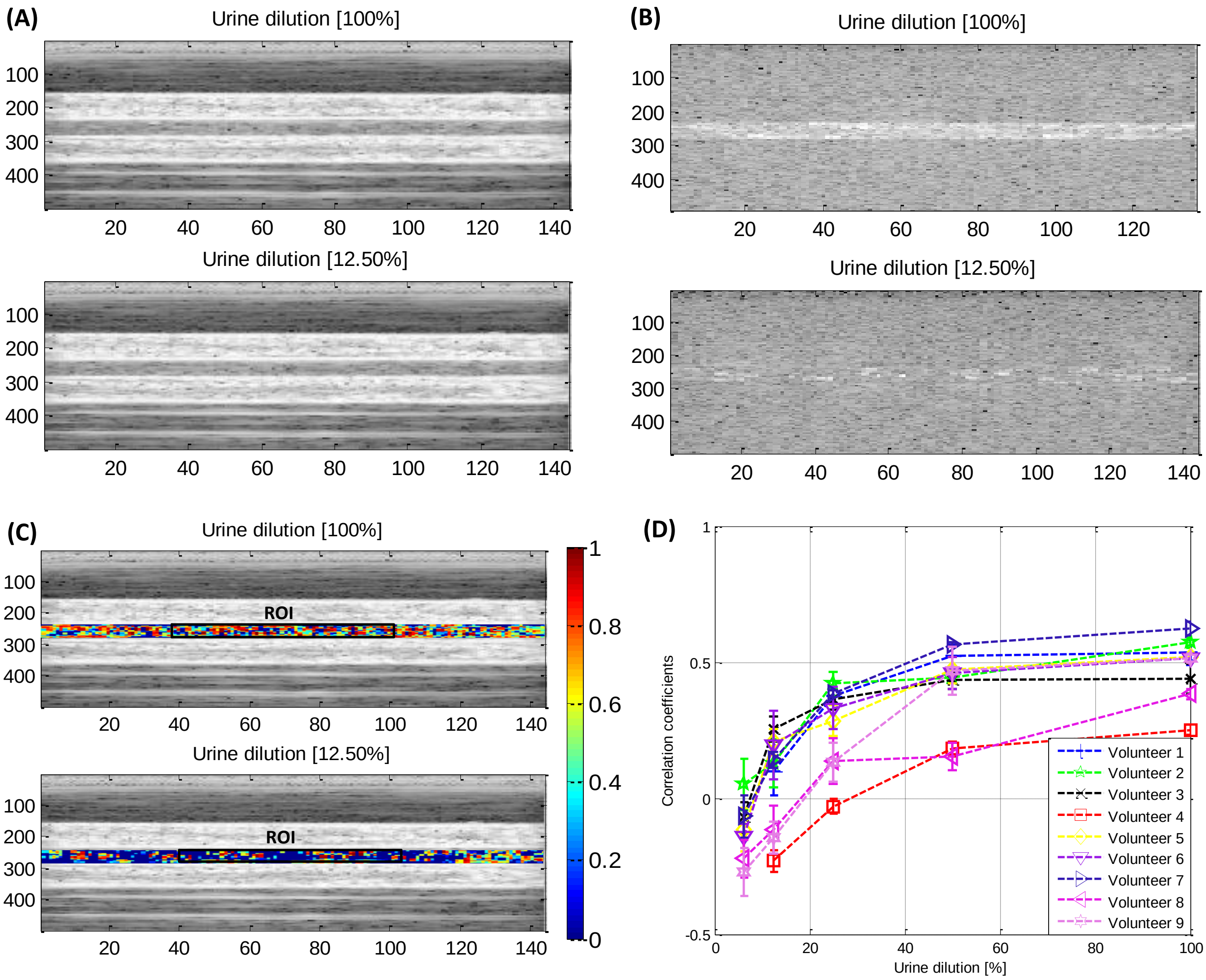

Figure 4: *Ultrasound images of the urethra model perfused with 100% (top) and 12.5% (bottom) urine solutions at a flow rate of 10ml/s (A) Before stationary echo cancellation. (B) after stationary echo cancellation. (C) Color coded correlation coefficients of flow through the urethra model perfused with 100% (top) and 12.5% (bottom) urine solutions at a flow rate of 10ml/s superimposed on ultrasound images. (ROI represents Region of Interest). (D) The average correlation values were plotted as a function of the urine dilution. The errorbars show average ±1 standard deviation in five frames.*

4. Discussion

The standard procedure to diagnose the cause of Lower Urinary Tract Symptoms (LUTS) is a urodynamic pressure-flow analysis. The invasive nature of the method makes it uncomfortable for patients and it may cause pain and acute urinary tract infection. A number of non-invasive techniques such as the condom-catheter method (12), the cuff method (13) and perineal sound recording (14) have been developed to diagnose BOO in patients with LUTS. However, as yet these methods cannot adequately replace the standard invasive diagnostic method. Conventional color Doppler US has also been proposed to non-invasively diagnose BOO (1). However, the narrowing in the urinary flow channel, can result in a disturbed urinary flow in the urethra, that is, a high flow velocity and/or turbulent urinary flow and conventional color Doppler is not suitable to quantify this disturbance. In cardiovascular research, decorrelation based flow estimation using US has been used to study the disturbance of flow in coronary arteries due to plaque formation. In a previous study, we showed the quantification of the decorrelation rate could be used to develop an US based non-invasive method for diagnosing BOO (15). The results showed at 2 cm downstream of the obstruction the decorrelation increased strongly with the degree of obstruction. This was possibly due to turbulence caused by the obstruction. Based on the theory of fluid flow we can expect that a higher degree of obstruction creates more turbulence in the urinary flow, which results in a higher decorrelation of US signals. However, the scatter particle concentration in urine may vary between persons and over time. This variation might affect the decorrelation process. Therefore to define the correct relationship between decorrelation and the degree of obstruction while correcting for differences in the concentration of scattering particles, we investigated in the present study the dependency of decorrelation on the scatter particle concentration using aqueous solutions with silica scattering particles and stepwise diluted urine samples.

In a urethral model the average correlation values with different scatter particle concentrations were calculated. The results show a steep increase of the average correlation values from low to intermediate concentrations and only a slight increase while reaching the high concentration. Therefore the use of varying, but sufficiently high particle concentrations may not have a significant effect on the decorrelation process. The correlation values at 100% urine dilution from most of the volunteers were in this range of sufficiently high particle concentration. Also the correlation coefficient at 50% urine concentration is nearly as high as at 100%. Therefore, we assume that in most individuals a second morning urine will be sufficient for a good measurement. This pleads for the applicability of the method. However, for two volunteers (4 and 8) the correlation values at 50% or more urine dilution were lower than those of the other volunteers (see Fig. 4(D)). This lower concentration was probably caused by the fact that these volunteers were drinking more fluid than the others, which resulted in already diluted urine. This was corroborated by the lighter color of these urine samples.

The average correlation values for different aqueous solutions with different scattering particle concentrations (mg/L) and diluted urine samples (%) were calculated. The transformation from dilution percentage (%) to mg/L of the diluted urine samples was determined using a conversion factor (equation 3) derived from the dependence of the average correlation coefficients on the silica gel particle concentrations. The expression to calculate the particle concentration from the correlation (equation 2) is valid when the calculated average correlation values are less than the value of the coefficient a in the experimental curve fitting. In case of higher values the expression will give a complex number. Ideally, at infinity the constant a and the calculated average correlation approach 1.

In practice, noise will sometimes cause the correlation to be higher than a. The multiple reflections of ultrasound signals inside the lumen of the phantom create a shadowing or ghosting artifact. This artifact results in a stationary echo pattern inside the lumen. The US filtering process by subtraction of subsequent signals not only removes this artifact but also causes a reduction in flow signal intensity. In case of low scattering particle concentrations this decrease significantly affected the correlation estimate. In the Figures 3(D) and 4(D), we can even see negative correlation values at low particle concentrations. Therefore, to avoid negative correlation values a minimum of 0.25 mg/L (See Fig. 5) particles should be present in the solution.

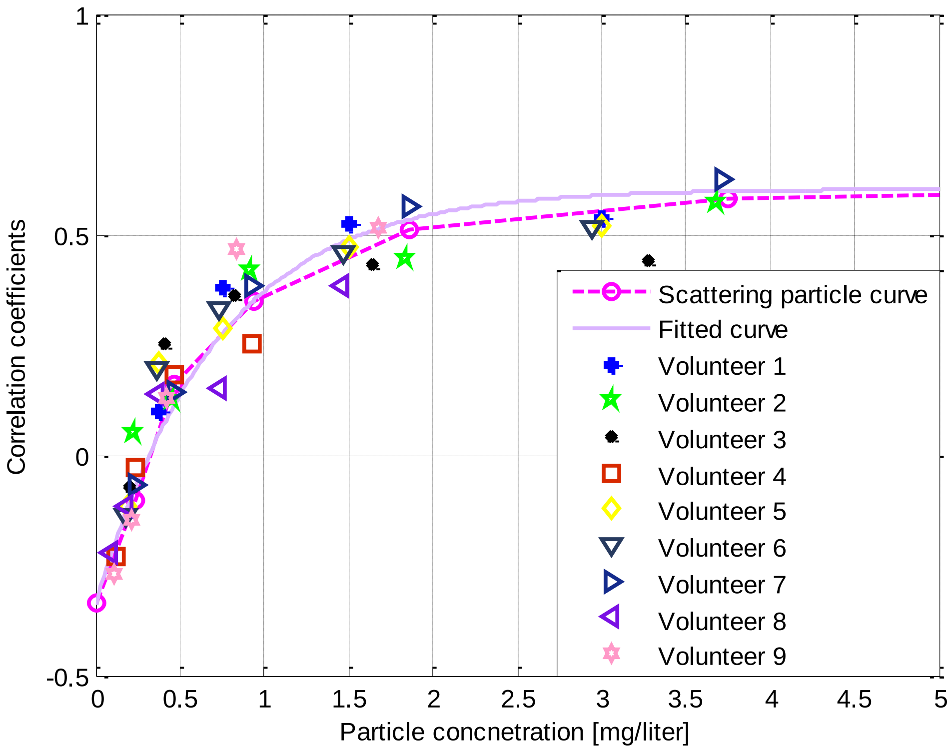

Figure 5: *The average correlation coefficients as a function of the scattering particle concentration in aqueous solutions and in volunteer urine samples. The dotted line represents the experimental data from tap water with added particles. The solid line represents the fitted curve to the volunteer data.*

As described before, the obstruction and high flow velocities in a phantom can create turbulence in the flow and can affect the decorrelation rate (15). Therefore, to study the influence of particle concentration on the decorrelation rate we kept the urinary flow in the experimental setting constant (10 mL/sec). However, a change in flow rate could also change the average correlation value. At lower flow rate values the change in the subsequent images will be small and they will be highly correlated. Whereas, at high urinary flow rates the correlation decreases. In reference (4) we have shown the relation between correlation and different flow velocities in obstructed and unobstructed urethra models.

To develop a complete technique the next step will be defining the relationship between the decorrelation of US signals and the Degree of Obstructions of the urethra models, while taking into account a suitable concentration of scattering particles. In a later phase, this relationship will be validated in a patient population and the decorrelation results will be compared with those of a pressure-flow study as the gold standard.

5. Conclusion

The estimation of the decorrelation rate between subsequent US images of disturbed urinary flow depends on the particle concentration in urine. The results of volunteer measurements indicate that generally morning urine contains sufficient scattering particles to be used for decorrelation imaging of urinary flow. This supports the potential use of the decorrelation method as a new non-invasive technique to diagnose BOO without correcting for differences in particle concentration.

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Appendix

correlation coefficients

The correlation coefficients $\rho_{i,j}$ between any two images were calculated as (16):

$$\rho_{i,j} = \frac{\sum_{n=1}^{N}\left[\left(S_i(n) - \bar{S_i}\right)\left(S_j(n) - \bar{S_j}\right)\right]}{\sqrt{\sum_{n=1}^{N}\left(S_i(n) - \bar{S_i}\right)^2 \sum_{n=1}^{N}\left(S_j(n) - \bar{S_j}\right)^2}} \tag{1}$$

where i =1,2…D-1 , j = 2,3…D. Where D is the number of US images (10), N is the number of image lines (144) in each image and $\bar{S}$ is the mean value.

Fisher Z-transformation

The correlation coefficients in each correlation image were transformed to a normal distribution using the Fisher Z-transformation defined as :

$$z = \frac{ln(1+\rho) - ln(1-\rho)}{2} \tag{2}$$

After transformation we calculated the mean $\bar{z}$ and transformed that back to the time domain by computing the inverse Fisher Z-transformation:

$$\bar{\rho} = \frac{e^{2\bar{z}} - 1}{e^{2\bar{z}} + 1} \tag{3}$$

Subsequently we took the average (ρ_{avg}) of all calculated mean correlation values $\bar{\rho}$ in each correlation image.

Chapter 4

Development of a non-invasive method to diagnose Bladder Outlet Obstruction based on decorrelation of sequential ultrasound images

Based on the publication:

Arif M Idzenga T, de Korte CL, van Mastrigt R. Development of a non-invasive method to diagnose Bladder Outlet Obstruction based on decorrelation of sequential ultrasound images. Urology 2015;85(3):648-52.

Abstract

Aims: To develop an ultrasound (US) based method for noninvasive diagnosing of bladder outlet obstruction, and the relationship between decorrelation of sequential US images and the degree of obstruction in a urethra model was studied.
Methods: A flexible model of a male urethra was constructed from 15% aqueous solution of polyvinyl alcohol cryogel. To create 4 different degrees of obstruction, polyvinyl alcohol rings representing the prostate were placed around the model. Each model was perfused at different flow rates (1-15 mL/s) with an aqueous solution containing scattering particles mimicking urine. At each flow rate, 10 sequential US images were acquired. The average correlation coefficients between the images were calculated and plotted as a function of the degree of obstruction and the flow rate.
Results: The average correlation decreased approximately linearly with an increase in the degree of obstruction. This decrease in correlation (decorrelation) might be due to turbulence caused by the obstruction. A higher degree of obstruction creates more turbulence and results in a higher decorrelation between sequential US images.
Conclusion: Quantification of the decorrelation between sequential US images may provide us with a new approach to noninvasively diagnose bladder outlet obstruction.

1. Introduction

A pressure-flow study is the standard procedure for diagnosing bladder outlet obstruction (BOO) in men with voiding symptoms (1). However, urethral catheterization may reduce the flow rate, increase the voiding pressure, and affecting the diagnostic result. The invasiveness of this procedure may also cause pain and increase the risk of urinary tract infection. As information about prostate size, flow rate, and postresidual volume is not sufficient to noninvasively diagnose BOO, the goal of many researchers has been to develop an accurate noninvasive urodynamic method for diagnosis. Although a number of such methods (2-4) to replace the standard invasive diagnostic method have been proposed, these methods are not yet routinely applied in clinical practice.

In a previous study (5), we applied a decorrelation method to Ultrasound (US) signals to estimate the urinary flow velocities in obstructed and unobstructed urethra models. This method compares the scatter pattern as generated by small particles between sequentially acquired US images. For laminar flow and at low flow velocities, the change in the scatter pattern between sequential images is expected to be small and the correlation between images consequently to be high. However, for turbulent flow and at high flow velocities, the change between sequential images is expected to be large and the correlation to be lower. This effect is called decorrelation.

Bonnefous *et al* (6) showed that the variance in blood flow downstream of a stenosis in the carotid arteries increases and that the decorrelation of US signals could be used to estimate the increase of variance. A similar phenomenon can be found in BOO (7). Obstruction can create turbulence in the urinary flow, which can affect the decorrelation. A higher degree of obstruction creates more turbulence and will presumably lead to a higher decorrelation between sequential images. The estimation of decorrelation of US signals caused by turbulence and high flow velocity may therefore provide a new noninvasive approach for diagnosing BOO. To test this hypothesis, we did an experimental study to relate decorrelation information to different degrees of obstruction in the urethra models.

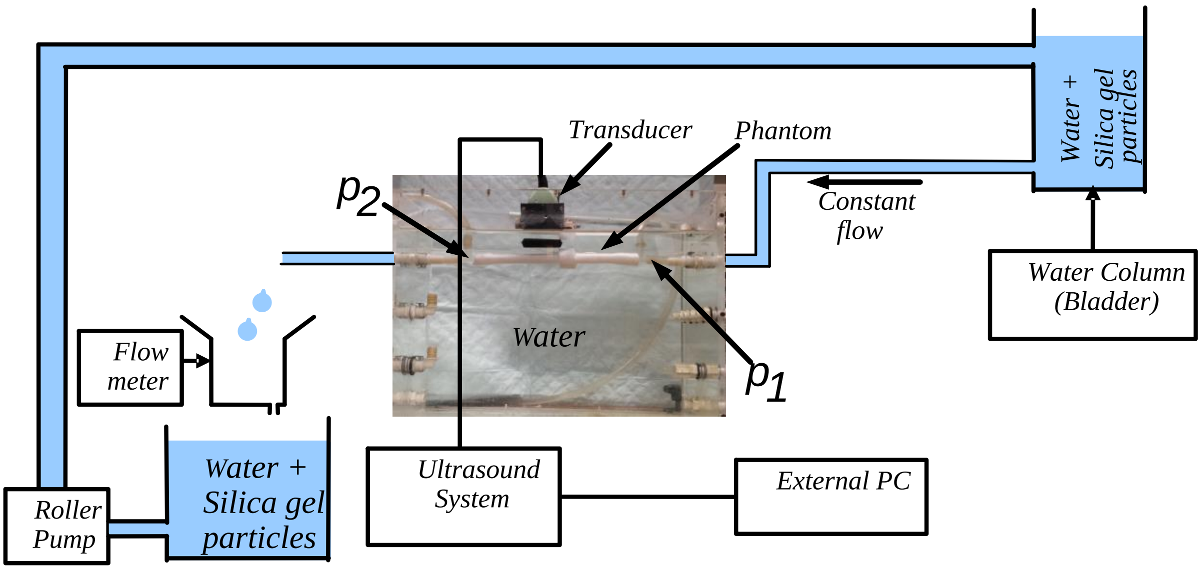

Figure 1: *Schematic drawing of the experimental setup.*

2. Materials and Methods

2.1 Urethra models

A 15% aqueous solution of polyvinyl alcohol (PVA) was used to make a flexible urethra model representing the lower urinary tract of a male patient (8). To construct the model, PVA solution was poured in a cylindrical mold (450 mm in length and 16 mm in cross-sectional diameter). A circular copper wire (5 mm in cross-sectional diameter) was placed along the center of the mold to create a flow channel in the model. To polymerize the PVA, the model was freeze-thawed once. In a freeze-thaw cycle, the mold was first stored in a freezer at -20^{o}C for 14 hours and then kept at room temperature (25^{o}C) for 10 hours. The number of freeze-thaw cycles controls the elasticity of the model (8). To create different degrees of obstruction, 4 flexible PVA rings (modeling the prostate) with internal diameters of 12, 9, 8, and 6 mm, and an external diameter of 29 mm were placed around the urethra model. The PVA rings were also polymerized using one freeze-thaw cycle.

2.2 Experimental Setup

The urethra model was placed in a water-filled container to prevent dehydration of the model. The water in the container also acted as US coupling medium (see Fig. 1). To generate flow, a water column was connected to the proximal end of the urethra model. The distal end was connected to an outflow tube draining into a fluid-filled expansion barrel via a rotating disk flow meter (DISA Electronic, Denmark). The fluid from the barrel was pumped back into the water column by a roller pump (SF-240; Verder B.V., The Netherlands). Pressure transducers were used to measure the pressures at the proximal (p_1)and distal (p_2) ends of the urethra model. Silica gel particles (50 mg/L) of size 15-40 mm (Sigma-Aldrich) were added to the water to mimic US-reflecting particles in the urine. The pressure drop ($p_1 - p_2$) over the model urethra at different degrees of obstruction caused by the PVA rings and the corresponding flow rates (1-15 mL/s) were recorded.

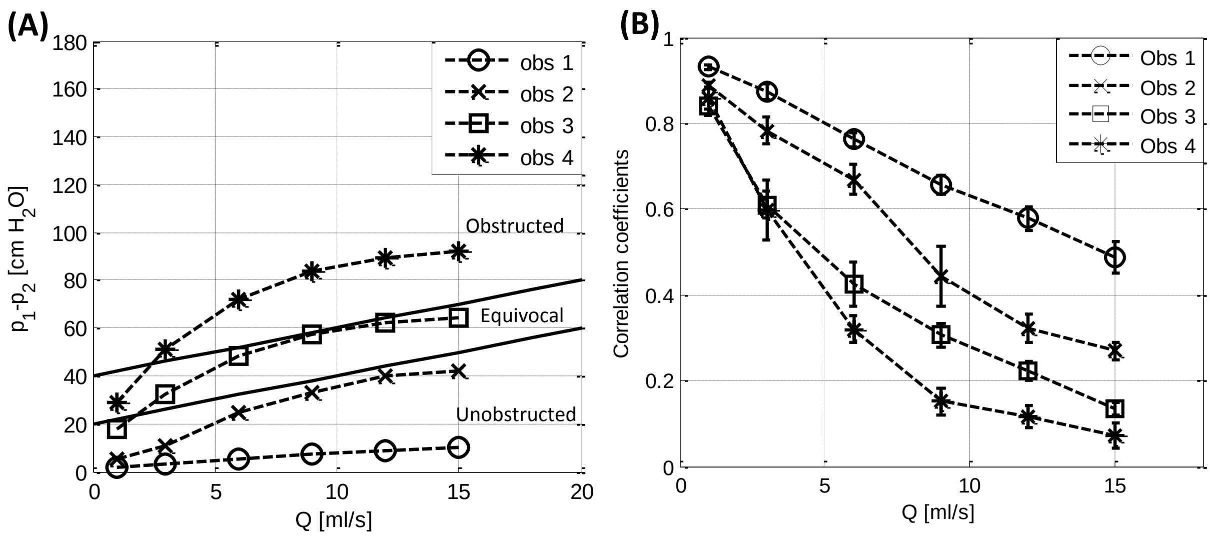

Figure 2: *(A) Pressure-flow plots of the four urethral models according to the International Continence Society (ICS) nomogram for obstruction and (B) the calculated average correlation coefficients of four degrees of obstruction in the region of interest (ROI) 3, plotted as a function of the applied flow rate.*

2.3 Data Acquisition

To acquire US data, a BK-Medical US system (Pro Focus UltraView 2202) equipped with a 5-MHz linear array transducer (8670) was used. We acquired 5 US frames at different pressure flow values for each degree of obstruction. Each US frame contained 10 sequential US images. Every image was constructed from 144 US radiofrequency signals acquired at a pulse repetition frequency of 5 kHz. Each radiofrequency signal yielded a single image line in an image. To get maximum reflection, the US transducer was positioned parallel to the flow direction with the US beam orthogonal to the flow. The US images were stored on an external personal computer and analyzed using custom written MATLAB (MathWorks, Natick, MA) programs.

2.4 Data Analysis:

A correlation method was applied to evaluate the changes in 10 sequential US images (9). To calculate the correlation coefficients between each pair of sequential images (ie, image 1 with image 2, image 2 with image 3, image 3 with image 4, and so forth), identical image lines were selected from the images. Next, segments of data points from both image lines were taken, and correlation coefficients between these segments were calculated. The correlation coefficient calculation process was repeated for all 144 image lines, and a correlation image was constructed, where each correlation value was represented by a color-coded value. From 10 US images, 9 correlation images could be constructed. To have a normal distribution of the correlation coefficients, the Fisher Z-transformation was applied (a detailed description is provided in Appendix, which has also been published in previous study (10)). In each correlation image downstream of the obstruction, 3 regions of interest (ROIs 1, 2, and 3) were selected. ROI 1 was started at 1 cm downstream of the obstruction and had a length of 1.5 cm. ROI 2 was adjacent to ROI 1 and also had a length of 1.5 cm, whereas ROI 3 combined ROIs 1 and 2. In each ROI, the mean correlation coefficient (ρ) value for each correlation image was calculated. Next, we took the average (ρ_{avg}) of these calculated mean correlation values and plotted it as a function of the degree of obstruction and of flow rate.

3. Results

The pressure-flow plots of the urethra models with the 4 PVA rings are shown in Figure 2(A). The pressure drop over the model increased with increasing flow rate for each model. The two straight lines represent the categorization of the pressure-flow data into unobstructed, equivocal, and obstructed voiding according to the International Continence Society nomogram of obstruction (1). The correlation coefficients of ROI 3 for the 4 models are plotted as a function of flow rate as shown in Figure 2(B). The curves decrease faster at a higher degree of obstruction. Examples of correlation images of the urethra models with the 4 PVA rings superimposed on separately collected B-mode images at a flow rate of 6 mL/s are shown in Figure 3. Flow is from left to right in the model, and the obstructing PVA ring is at its left side. The change in average correlation coefficients in ROI 3 with the 4 degrees of obstruction at different flow rate values is shown in Figure 4(A) and those for ROIs 1 and 2 are shown in Figure 4(B) & 4(C). The results show that the average correlation values decrease approximately linearly with increasing degree of obstruction at each flow-rate value.

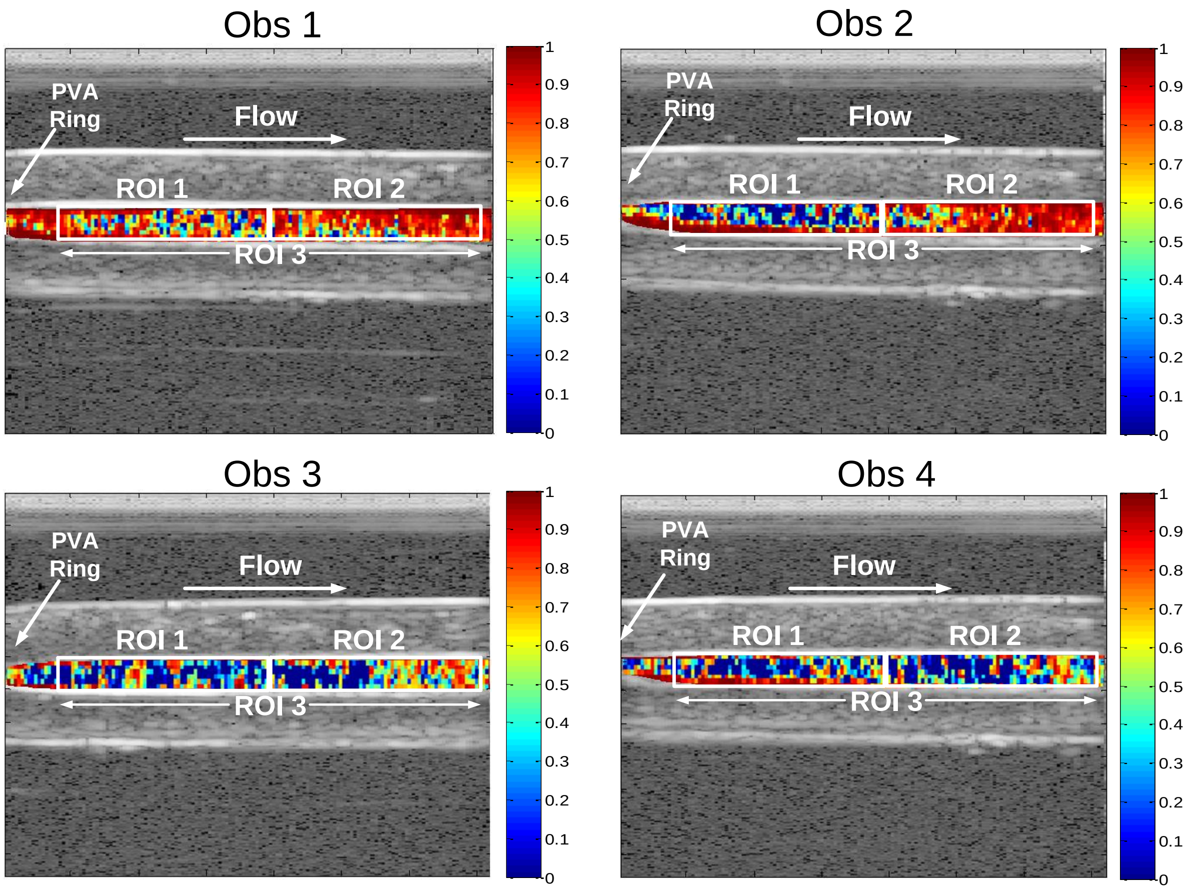

Figure 3: *Example of correlation images of 4 urethral models with 4 degrees of obstruction superimposed on separately collected B-Mode images at a flow rate of 6 mL/s. The three regions of interest (ROI) are also shown.*

4. Discussion

BOO is common in elderly men and can result in lower urinary tract symptoms including hesitation, a weak urinary stream, nocturia, and dribbling. Because the invasive nature of a standard pressure-flow study to diagnose BOO is uncomfortable to the patient, a simple non-invasive diagnostic method is needed. To develop a new noninvasive approach to diagnose BOO, we therefore implemented a correlation-based method on sequentially acquired US data. We constructed a urethra model, applied 4 degrees of obstruction, and implemented this method. Figure 2(A) shows the pressure-flow plot of our urethra model and the categorization of the data into unobstructed, equivocal, and obstructed voiding according to the International Continence Society nomogram for obstruction. The plot shows that the pressure-flow relation in our model for each degree of obstruction is not in accordance with the linear relationship assumed in the definition of Blader Outlet Obstruction Index (BOOI) (11). This is because the human urethra is very elastic and has an opening pressure that should be exceeded before urinary flow starts. As our model is also elastic but has no such opening pressure, the pressure-flow plot of each degree of obstruction crosses the two straight lines that delineate the obstruction categorization. For this reason, we did not use BOOI to characterize the degree of obstruction of our models and named them degrees of obstruction 1-4.

Idzenga *et al* (12) showed that audible sound produced by turbulence downstream of an obstruction in a urethra model is related to the degree of obstruction. Similar results were found in our model study, in which decorrelation caused by turbulence increases with the increase in the degree of obstruction. In the correlation analysis, we calculated the average correlation coefficients in the 3 ROIs for each urethra model at different values of flow rate (1-15 mL/s). For ROI 3, the largest region, results indicate that because of turbulence caused by the obstruction, the correlation curves decrease evenly with the degree of obstruction (see Fig. 2(B)). In ROI 1, the first half of ROI 3 and immediately downstream of the obstruction, the decorrelation for each degree of obstruction is higher than that in ROI 2, which is the second half of ROI 3 (see Fig. 4(B) & 4(C)). This can be explained by the higher turbulence level in ROI 1 caused by the obstruction in the urethra model. In ROI 2, located further downstream of the obstruction, the turbulence is less and the flow becomes laminar. However, as the degree of obstruction increases, the length of the turbulent flow region also increases, and the correlation values in ROI 2 decrease faster. In Figure 3, it can also be seen that the correlation values in ROI 2 are higher (close to 1) in degrees of obstruction 1 and 2 than in degrees of obstruction 3 and 4. The correlation values also decrease (close to 0), if the degree of obstruction increases. The result shows that the average correlation values decrease more smoothly in ROI 3 than in ROIs 1 and 2, possibly due to averaging over a larger region. In the in vivo measurements, the optimal ROI will have to be adjusted.

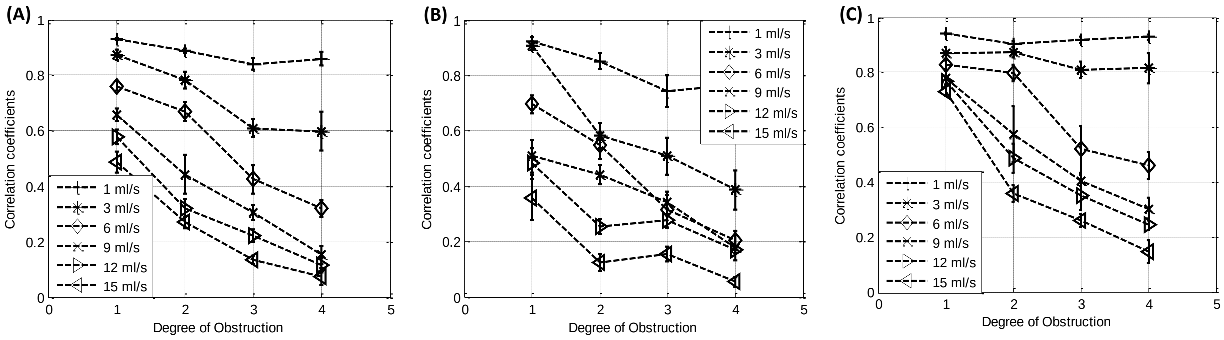

Figure 4: *The calculated average correlation coefficients in (A) region of interest (ROI) 3, (B) ROI 1, and (C) ROI 2 plotted for six different flow rates as a function of the four different degrees of obstruction.*

Ozawa *et al* (13) used Doppler ultrasonography to measure the urinary flow velocity in the urethra. In a small patient population, they showed that the ratio of flow velocity values at two different positions, downstream of the obstruction and in the obstruction, could be used to diagnose BOO. However, high urinary flow velocities (up to 300 cm/s) have been reported in the literature (14, 15). The aliasing effect that can occur at such high urinary flow velocities limits the use of Doppler ultrasonography. Decorrelation also depends on flow velocity. Although, typical flow-rate values in clinical practice are relatively low in patients with BOO, the flow velocity values might still be high because the obstruction reduces the cross-sectional area and results in higher flow velocities. As we showed in a previous study (5) that the decorrelation of US signals can be used to estimate high urinary flow velocities in obstructed urethra models, the results of this study therefore support the use of the decorrelation method rather than the color Doppler method for urinary flow imaging in BOO patients. The present study shows that the decorrelation of US signals downstream of an obstruction in a urethra model is induced by turbulence and related to the degree of obstruction.

To apply this approach in clinical practice, initially US correlation data will be collected from healthy volunteers at different values of flow rates and flow velocities. Next, a study will be performed in patients with BOO, and the decorrelation results will be compared with pressure-flow studies to estimate the diagnostic power.

5. Conclusion

In our urethra model, the decorrelation between sequential US images increased with an increasing degree of obstruction. Therefore, the quantification of decorrelation between sequential US images could be a new technique to noninvasively diagnose BOO.

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PART III

IN-VIVO STUDIES

Chapter 5

Diagnosing bladder outlet obstruction using non-invasive decorrelation based ultrasound imaging: A feasibility study in healthy male volunteers.

Based on the publication:

M. Arif, Tim Idzenga, Chris L. de Korte and Ron van Mastrigt, 'Diagnosing bladder outlet obstruction using non-invasive decorrelation based ultrasound imaging: A feasibility study in healthy male volunteers'. Ultrasound in Med. & Biol, 2015 Dec 41(12):3163-71.

Abstract

Aims: A feasibility study on the applicability of an ultrasound decorrelation method to urinary flow imaging was carried out in 20 healthy male volunteers, to provide a basis for a non-invasive approach to diagnose bladder outlet obstruction.
Methods: Each volunteer voided five times in a flow meter in standing position. During each voiding, ultrasound radiofrequency frames were acquired transperineally at different flow rates.
Results: The results indicated that the decrease in correlation (decorrelation) of ultrasound radiofrequency signals had no unique relation with flow rate, but decreased distinctively with urinary flow velocity. In most of the healthy volunteers, the decorrelation was small because of the low flow velocity. However, because of the different flow velocities in volunteers, the variation in slope between volunteers was statistically significant.
Conclusion: Therefore, it is probably possible to use the decorrelation method to differentiate between healthy persons and patients with obstruction.

1. Introduction

Bladder outlet obstruction (BOO) is a common urologic condition in elderly men. Lower urinary tract symptoms (LUTS), including post-void residual volume, low urinary flow rate and nocturia, are common symptoms of BOO. Urodynamic pressure–flow studies are accepted as the standard procedure to diagnose BOO (1). A major disadvantage of this method is that it involves urethral catheterization, which causes partial obstruction during micturition and may alter the diagnostic results. The invasive nature of the method also causes discomfort and pain to the patients and might result in infection. Therefore, the development of a noninvasive, but accurate urodynamic method of diagnosing BOO has been the goal of many urodynamic experts.

To develop such a clinical urodynamic method, we applied a non-invasive ultrasound (US) decorrelationbased technique to quantify flow velocity and turbulence in silica gel urethra models (2, 3). This technique estimates the decrease in correlation (decorrelation) between sequentially acquired US radiofrequency (RF) signals reflected by small scattering particles. In urine, various types of crystals such as calcium oxalate, uric acid and amorphous urates have been identified (4, 5). These crystalline structures can act as small ultrasound scattering particles in urine. We reported that morning urine contains a sufficient concentration of these scattering materials and is suitable for US imaging of urinary flow using the decorrelation method (6). The studies indicated that the decorrelation depends on the urine flow velocity and turbulence caused by urethral obstruction (2, 3). Decorrelation also increased with the degree of obstruction (3).

On this basis we hypothesized that it might be possible to develop a practical method for noninvasively estimating the degree of obstruction in male patients with lower tract symptoms. For a number of reasons it was necessary to test this hypothesis in healthy volunteers. First, it was not at all obvious if we could acquire images of the lower urinary tract of males during voiding of sufficient quality to enable decorrelation analysis and how the tract should be approached, for example, rectally, abdominally or perennially. Second, for practical measurements in patients, it was necessary to develop a procedure and device to image the tract during voiding. Therefore a remote manipulator was developed and repeatedly tested to correctly aim the transducer during voiding. Ethically it would be unacceptable to develop and test this method in patients before a thorough evaluation in healthy volunteers. Additionally, baseline measurements in healthy subjects were required for interpretation of results in patients. In this article we report a study in healthy male volunteers on the applicability and reproducibility of a non-invasive US decorrelation method. For this purpose, we studied the variability in decorrelation values between and within healthy volunteers at maximal and submaximal flow rates and different flow velocities.

2. Materials and Methods

2.1 Population

After institutional research ethics board approval (MEC-2013-419), we recruited 20 healthy male volunteers to void at least five times at normal desire. At recruitment, the volunteers gave their informed consent and were asked to complete an International Prostate Symptom Score (IPSS) form to quantify their urologic condition (7).

2.2 Experimental Setup

The volunteers voided in a standing position with an ultrasound transducer placed gently against the perineum using a specially designed mechanical transducer manipulator (Fig. 1). To adequately visualize the urethra, the transducer was manually moved in angular and sidewise directions by the investigator using the vertical handle. The vertical position was adjusted by moving the junction C1. To acquire US RF data of the urinary stream, a BKMedical US system (Pro Focus UltraView 2202) with a custom-designed RF interface was used. The US system was equipped with a 5-MHz linear array transducer (8670), consisting of 128 transducer elements with a pitch of 0.3 mm. The acquired RF signals were stored on an external PC using a frame grabber (OR-X4 C0-SE-F00, Imago Group, Waalre, Netherlands). The RF data were acquired at a sampling frequency (fs) of 20 MHz. The flow rate was measured with a rotating disk flow meter (Disa Electronic, Denmark) and stored on a PC using an analogue-to-digital (A/D) converter (PCI 6220, National Instruments,Woerden, The Netherlands) in combination with a custom-written LabView program (National Instruments, Woerden, Netherlands). During US data acquisition, a light-emitting diode on the frame grabber emitted light (flashes) at a frequency of 16 Hz. A photo-detector was used to record this signal via the A/D converter and the LabView program to synchronize US data with the flow rate signal. The voided volume was measured at each voiding using a measuring jug.

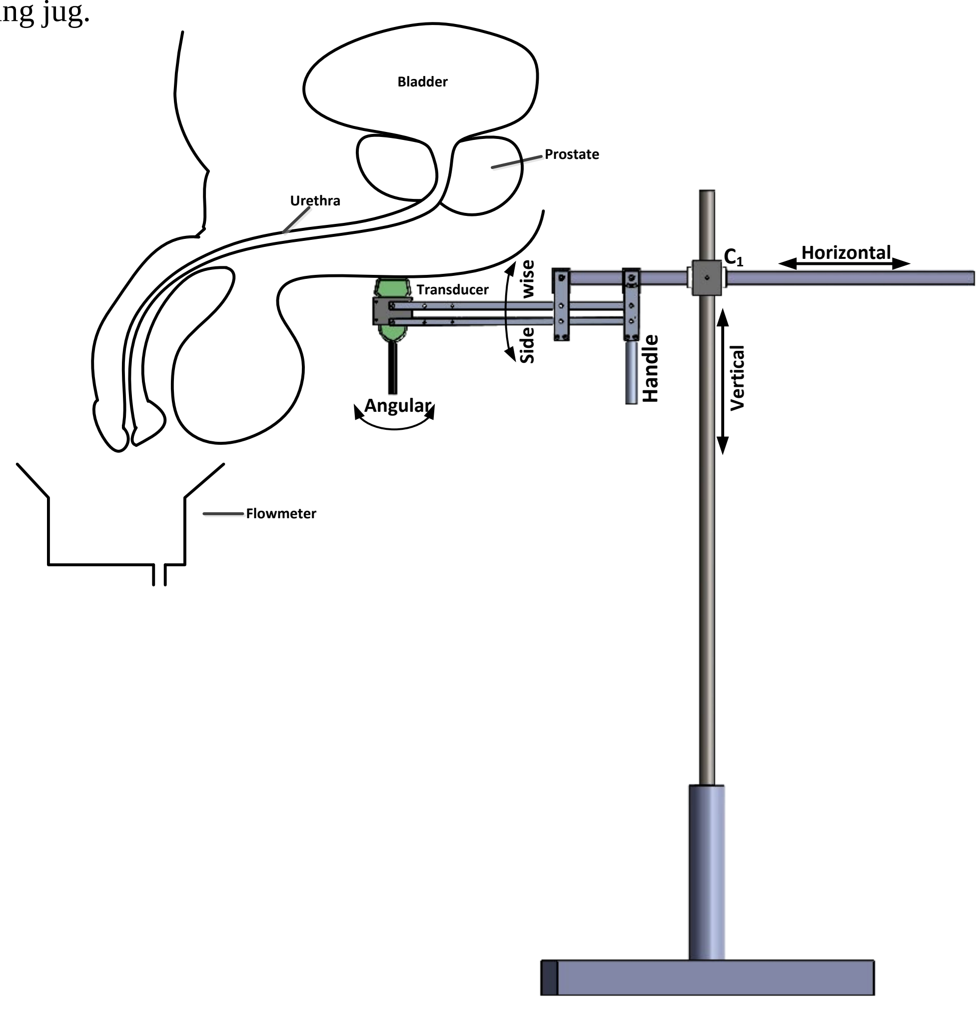

Figure 1: *Experimental setup. The position of the ultrasound transducer position was controlled by a specially designed manual probe manipulator.*

2.3 Data Acquisition

We acquired 50 ultrasound frames at the frame rate of 10 frames/s at maximum and sub-maximum flow rates during each voiding of each volunteer. Each US frame contained 10 sequential RF data sets (images). Every RF data set consisted of 144 RF signals acquired at a pulse repetition frequency (PRF) of 0.5 kHz. Each RF signal yielded a single image line in an image. The US frames were stored on an external PC and analyzed using custom-writtenMATLAB (The MathWorks, Natick,MA, USA) programs.

2.4 Data Analysis:

2.4.1 ***Correlation coefficients.*** In healthy volunteers, because of their low flow velocity, the decorrelation between sequential US signals was very small. Therefore, to adequately estimate the decorrelation we calculated the correlation coefficients (ρ) between the RF data sets at an interval longer than that used in our earlier measurements in urethra models (data set 1 with 5, data set 2 with 6, data set 3 with 7, etc.), instead of subsequent RF data sets (data set 1 with 2, data set 2 with 3, etc.). To do this, segments of data points from two RF lines representing a certain echo depth were taken, and the correlation coefficients between these segments were calculated. This was repeated for all image lines of the full data set, and a correlation coefficient distribution (correlation image) was constructed by using a color code for each correlation value (a detailed description of the correlation coefficient calculation has been given in (2)). For each US frame, from 10 ultrasound RF data sets, 6 correlation images were thus constructed. To calculate averages, a normal distribution of the correlation coefficients was obtained by applying the Fisher Z-transformation (8).

Table 1: *International Prostate Symptom Scores and urodynamic parameters.*

Volunteer	IPSS Score	Attempted voidings	Successful voidings	Average Urine Volume of 5 voidings (mL)	Average maximum Flow rate of 5 voidings (mL/s)
1	3	6	5	239	17
2	0	5	5	375	25
3	1	8	5	338	14
4	4	5	5	669	20
5	2	6	5	432	27
6	4	6	5	611	37
7	1	6	5	261	24
8	2	5	5	574	28
9	0	7	5	520	42
10	0	5	5	360	25
11	3	7	5	665	26
12	4	5	5	437	16
13	12	6	5	574	37
14	0	5	5	259	20
15	9	5	5	534	33
16	0	5	5	238	11
17	2	5	5	266	15
18	0	5	5	449	28

IPSS = International Prsotate Symtoms Score

After transformation, we calculated the mean $\bar{z}$ in a region of interest (ROI) of length 1.8 cm selected in each correlation image downstream of the prostatic urethra and transformed it back to $\bar{\rho}$ by computing the inverse Fisher Z-transformation. Next we calculated the average (ρ_{avg}) of these $\bar{\rho}$ values over the six correlation images for each US frame.

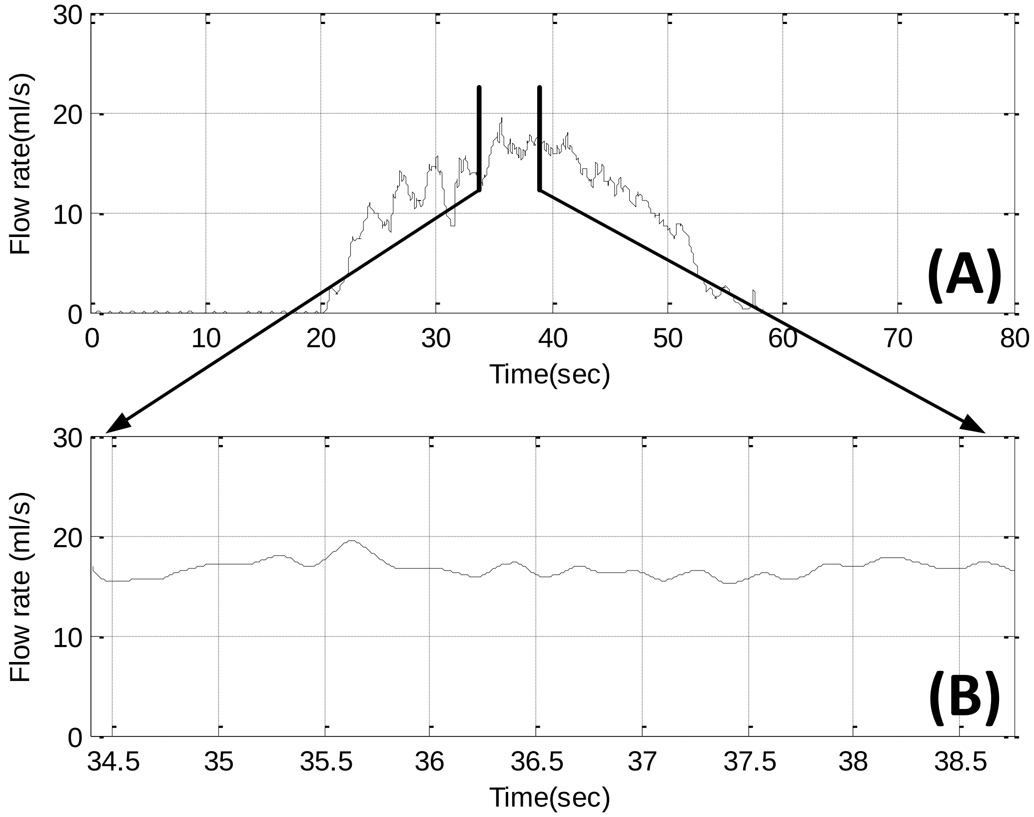

Figure 2: *Typical flow rate curve of a volunteer as a function of time (A) and enlarged view of data acquisition time (B).*

As we acquired US frames at different flow rate values during a complete voiding cycle, we obtained ρ_{avg} values at each of these flow rates and flow velocities for each volunteer. The flow velocity v (cm/s) in the urethra corresponding to each measured flow rate $\mathrm{Q_m}$ (ml/s) value was calculated using the relation, $v = \mathrm{Q_m}/A$, where $A\ (cm^2)$ is the cross-sectional area of the urethra, which was calculated using the relation $A = \pi\left(\frac{D}{2}\right)^2$, where $D(cm)$ is the diameter of the urethra measured at the center of the ROI using the ultrasound system.

2.4.2 ***Decorrelation-flow velocity relationship***: To calculate the change in correlation with flow velocity for all volunteers, we interpolated the correlation data of each volunteer to derive correlation coefficients at discrete flow velocity values $v(k)$, where k = number of volunteers. We calculated the averages of the interpolated correlation data and plotted these as a function of flow velocity. To determine the relationship between decorrelation and urinary flow velocity, a non-linear least squares power law model was used to fit the equation

$$\rho_{avg}(k) = a\,.\,\{v(k)\}^b + c \qquad (1)$$

to the average interpolated correlation values for all volunteers. Here a, b and c are constants. To validate the relationship between decorrelation and urinary flow velocity, a blinded observer was asked to independently measure the diameter (D) and cross-sectional area (A) of the urethra at the center of the ROI for each voiding. From this cross-sectional area A and the urinary flow velocity values calculated from the ρ_{avg} for each volunteer using eqn (1), we calculated the flow rate (Q_c), and compared it with the measured flow rate values (Q_m) of each voiding from each volunteer. A linear fit with 95% confidence interval was used to quantify the level of agreement between Q_c and Q_m.

2.4.3 *Statistical analysis*: For each volunteer we measured one voided urine volume and one maximum urinary flow rate in each measurement, but the average correlation values (ρ_{avg}) were calculated at different (maximum and sub-maximum) flow rates and flow velocities during a complete voiding cycle. For each ρ_{avg} value, we calculated the slope as,

$$Slope = \frac{\rho_{avg} - 1}{v} \quad (2)$$

To calculate if volunteers had statistically significant different parameter values we applied one-way analysis of variance (ANOVA) to normally distributed data (urine volume and flow rate) and the Kruskal–Wallis test to non-normally distributed data (slope) in SPSS (IBM, Armonk, NY, USA). The Kolmogorov–Smirnov normality test was used to examine the distribution of the voided volume, urine flow rate and slope.

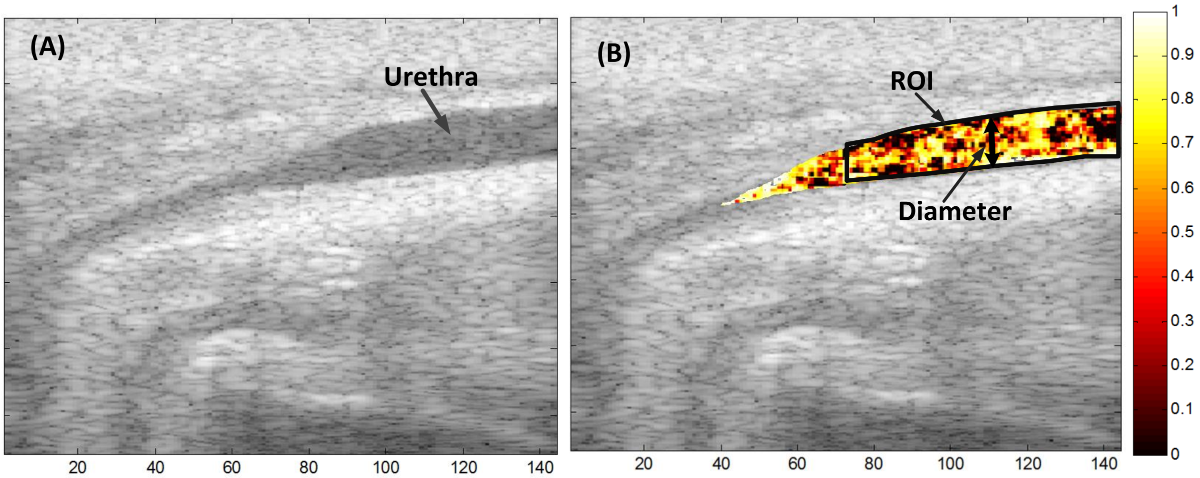

Figure 3: *(A) Example of in vivo B-mode ultrasound image of the urethra during voiding of a healthy volunteer. (A) Correlation coefficient distribution overlaid on the B-mode ultrasound image. The ROI and the measured urethra diameter are also shown. In both images, urine flows from left to right. ROI = region of interest.*

3. Results

3.1 Population

For 18 of 20 volunteers, we were able to successfully record urinary flow data. Two volunteers were not able to void in the experimental setting. The average voided urine volume, average maximum flow rate of five voidings and IPSS of the remaining participants are shown in Table 1. The IPSS values revealed the healthy urologic condition of most volunteers. IPSS values from 1 to 7 correspond to mild symptoms, values from 8 to 19 correspond to moderate symptoms and values from 20 to 35 correspond to severe symptoms (7). The IPSS values for volunteers 13 and 15 were in the moderate range. This was due to their high voiding frequency (every 2 h), as these two volunteers were drinking more fluid than the others.

3.1 In-vivo results

Figure 2(A) is a typical urinary flow rate curve of a volunteer. The flow rates corresponding to the data acquisition time are provided in Figure 2(B). Figure 3(A) is an in vivo US B-mode image of a urethra during voiding. The correlation image constructed from the first and fifth US RF data sets generated by the motion of the urine is overlaid on the US B-mode image in Figure 3(B). The ROI downstream of the urethra is also shown. In Figure 4 are plots of calculated ρ_{avg} values as a function of flow rate and flow velocity for each volunteer. Figure 4(A) reveals that the correlation coefficients and flow rates do not appear to be uniquely related. However, a unique relationship was observed between correlation coefficients and urinary flow velocity (Fig. 4(B)).

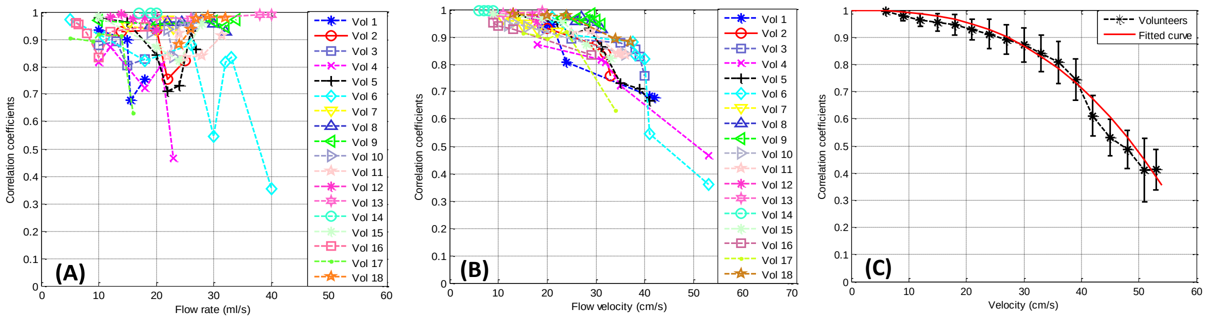

Figure 4: *Average correlation coefficients calculated for volunteers are plotted as a function of flow rate (A) and flow velocity (B). (C) Means and standard deviations of interpolated correlation coefficients of all volunteers as a function of flow velocity.*

3.2 Decorrelation-flow velocity relationship

In Figure 4(C), we plotted means and the standard deviations of interpolated correlation coefficients at discrete values of flow velocity for all volunteers. The fitted curve is also shown. The R-square value (0.98) of the fitted curve indicates that the decorrelation was strongly related to urinary flow velocity. Using equation (1) we could calculate these flow velocities from the ρ_{avg} values of each volunteer using constants a (20.000013), b (2.71) and c (0.99).

Figure 5 depicts the variations in the calculated flow rate $(Q_c)$and measured flow rate Q_m for each voiding in all volunteers. The R-square value of the linear fit was 0.63 with a 95% confidence interval of 4.58–4.62.

3.3 Statistical Analysis Results

Results of the statistical analysis are outlined in Tables 2 and 3. There are statistically significant differences (p value < 0.001) between volunteers in all parameters. The normality test indicated that the voided urine volume (p value = 0.057) and urine flow rate (p value = 0.083) were normally distributed, but the slope (p value = 0.002) was not normally distributed.

Table 2: *Results of variance analysis (one-way analysis of variance) using maximum urinary flow rate and voided urine volume measured for each participant.*

Voided Volume:			
Between volunteers	17	7.7	<0.001
Within volunteers	72		
Total	89		
Urine Flow rate:			
Between volunteers	17	32.9	<0.001
Within volunteers	72		
Total	89		

Table 3. *Results of non-parametric (Kruskal–Wallis) test to determine the statistical significance of differences in slopes between participants.*

Kruskal Wallis :	**Degrees of freedom**	**Chi- Square test**	**Significance**
Ultrasound Slope:	17	75.3	<0.001

1. Discussion

The aim of this study was to apply the US decorrelation method in healthy male volunteers. Currently, an invasive urodynamic pressure–flow study is the procedure routinely used to diagnose BOO. The invasive nature of such a pressure–flow study is uncomfortable to the patient; therefore, a simple non-invasive diagnostic method is needed.

Ozawa (9) used color Doppler US to measure urinary flow velocity in patients with BOO and compared their results with those of a pressure–flow study. They measured urine flow velocity transperineally in the distal prostatic urethra just above the external sphincter and in the sphincteric urethra. In the study of 22 men, a velocity ratio cutoff point of 1.6 was defined as differentiating between healthy and obstructed patients. However, high urinary flow velocities (≤300 cm/s) have been reported in the literature (10, 11). Urethral obstruction reduces cross-sectional area and may result in even higher urine flow velocities, which can create turbulence. Continuous wave Doppler can also be used to detect high urinary flow velocities, but does not provide spatial information or allow 2-D visualization. With pulse wave (PW) Doppler, this is feasible, but at very high flow velocities and/or in the presence of turbulent flow, aliasing can occur, as illustrated in Figure 6. Because of the aliasing effect, urinary flow velocity cannot be quantified and the relation between aliasing and flow velocity cannot be defined using PW Doppler. The decorrelation method can be used to measure such high urinary flow velocities because it is not affected by aliasing. Although Doppler US imaging can very accurately measure local flow velocities, it provides the best results when the angle between flow and the US beam is less than 65°. In patients, because of the curvature of the urethra, the angle between flow and the US beam exceeds 65°, and measurement of urinary flow velocity in the distal urethra (part of the urethra after the prostate) using Doppler US is very difficult, as we see in Figure 6. The decorrelation method, on the other hand, gives a better estimate of flow at angles close to 90° and, therefore, is more suitable for imaging of the distal urethra. In the study reported here, the application of an US decorrelation-based method was tested in healthy male volunteers, and a relation between decorrelation and urinary flow velocity was determined. We acquired US RF data of urinary flow from 18 healthy male volunteers at different values of flow rate and corresponding flow velocity. Figure 4 illustrates that there was no unique relationship between correlation values and flow rates; however, the decrease in correlation with flow velocity was very distinct. Li (12) reported that in a plastic arterial phantom, the decorrelation is directly related to the displacement of particles and, thus, to velocity. For a constant cross-sectional area A, flow velocity increases with an increase in flow rate and, thus, causes an increase in decorrelation. However, because of the viscoelastic properties of the urethra, the cross-sectional area of the urethra may also increase with an increase in flow rate and may cause the flow velocity to decrease, remain constant or increase slightly. Therefore, the relation between decorrelation and flow rate is not as strong as that between decorrelation and flow velocity. As we can see in Figure 4b, the flow velocity values measured in most of the healthy volunteers were low and the correlation was high. Although typical flow rate values in clinical practice are relatively low in patients with BOO, flow velocity values and/or turbulence effect in the flow might still be high because of the obstruction and result in a higher decorrelation rate. Therefore, the results of this study support the use of the decorrelation method to diagnose BOO in patients.

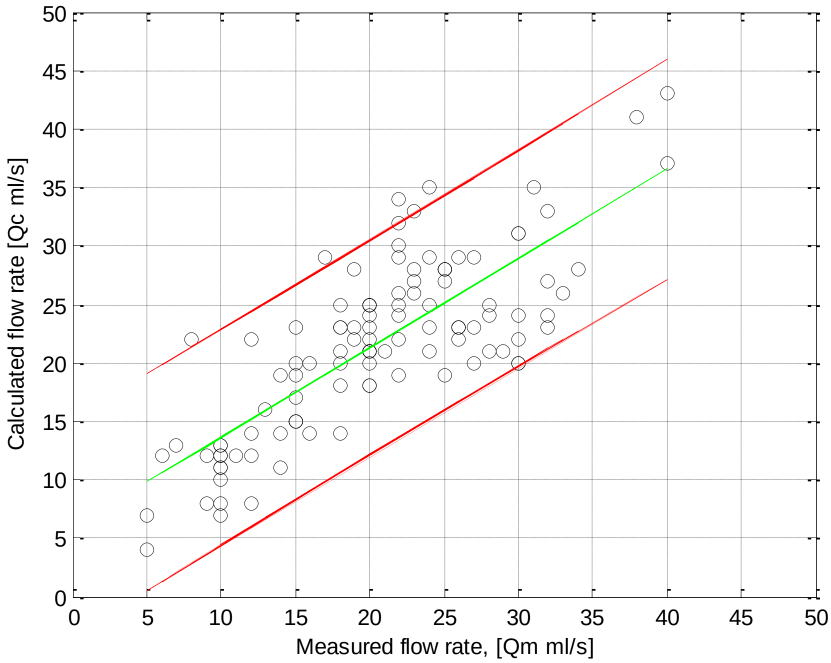

Figure 5: *Variation in calculated flow rate* (Q_c) *and measured flow rate* Q_m *for all volunteers. Several measurements at different flow rates are plotted for each volunteer. A linear polynomial fit between* (Q_c)*and* Q_m *with 95% confidence interval is also shown.*

In the previous urethra model study (2), we reported that for high flow velocities (≤300 cm/s), the decrease in correlation is related to velocity. In this study, we obtained similar results for a lower range of urinary flow velocities (0–50 cm/s). Decorrelation between sequential US signals decreases with decreasing flow velocity and increases with decreasing PRF. Therefore, to calculate decorrelation at low flow velocities in healthy male volunteers, we used a PRF lower (0.5 kHz) than that (9 kHz) used in earlier urethra model studies. In patients with BOO, the flow velocities may be higher, which would require readjustment of the PRF.

We tried different mathematical models, such as linear, cosine, second-order polynomial and power law models, to fit the decorrelation–flow velocity relationship. The power law model gave the best fit to our experimental results. The theoretical value of c should be 1, and the value of c 5 0.99 in our experimental results is close to this theoretical value.

The decorrelation–velocity relationship depends on the characteristics of the ultrasound system. The literature (12, 13) indicates that the rate of decorrelation between sequential ultrasound RF signals is a function of flow velocity, pulse repetition interval (PRI) and beam characteristics of the transducer. In an ultrasound system, by varying the f-number, one can adjust the beam characteristics and the decorrelation rate. To calibrate the decorrelation properties and to find a suitable decorrelation–velocity relationship independent of the imaging system, similar values for f-number, PRI and central frequency of the US system should be applied.

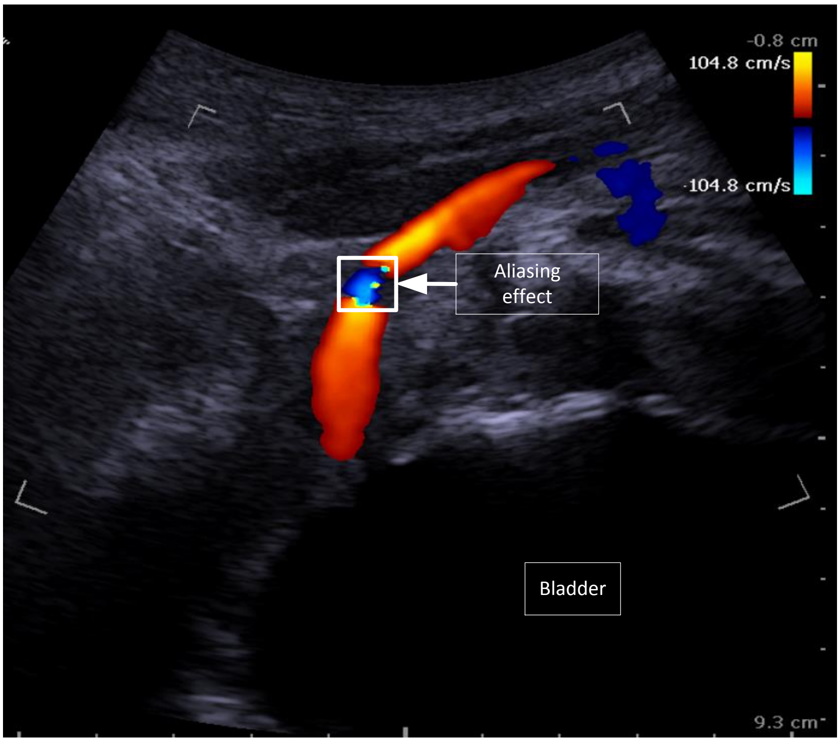

Figure 6: *Color Doppler ultrasound image of urinary flow in a healthy man. The color bar represents the measured flow velocity values. The maximum of the scale for measured flow velocity was at 104.8 cm/s. Red and blue represent flow toward and away from the transducer. At the external sphincter, an aliasing effect caused by the higher urinary flow velocity is seen.*

A linear relationship between the flow rate (Q_c) calculated from the decorrelation values measured in volunteers and the measured flow rate (Q_m) can be seen in Figure 5. In an ideal situation, the calculated flow rate should be identical to the measured flow rate. In practice, several errors cause deviations. One of these is the fact that in the calculated flowrate a uniform velocity profile is assumed, which is not realistic. Another error may be caused by variation in the position at which the blinded observer has measured the diameter and cross-sectional area. The fitted relation used to estimate velocity from decorrelation could also be a source of error.

To successfully acquire US data on urinary flow, the transducer position against the perineum is very important. We acquired 10 frames (each consisting of 10 data sets) per second. The 10 subsequent echo lines that were used for the decorrelation estimation were acquired at a PRF of 5 kHz. Therefore, minor motions of the transducer will be much smaller than the particle motion and, consequently, will have only a minor effect on the decorrelation. For each volunteer, the numbers of attempted and successful voidings are listed in Table 1. Unsuccessful voidings were sometimes due to wrong positioning of the transducer or to movement of the volunteer during voiding. To avoid this, patients were allowed to urinate in a sitting position instead of standing.

The outcome of the statistical analysis in Table 3 indicates that there was a significant difference in slope between volunteers. In the male volunteers, slope depends on flow velocity. In the patients with BOO, flow velocity is expected to be higher as a result of the obstruction. Therefore, it might be possible to use the decorrelation slope as a non-invasive diagnostic measure of BOO. We will explore this in a subsequent clinical study.

4. Conclusion

The decorrelation of sequential US signals is uniquely related to urinary flow velocity but, not urinary flow rate. The variability in slope in male volunteers depends on flow velocity. Because of the different flow velocities in the volunteers, the variability in slope between volunteers was statistically significant. In patients with BOO, flow velocities are expected to be high as a result of the obstruction. Therefore, estimation of US decorrelation could provide a non-invasive approach to differentiate between healthy volunteers and obstructed patients.

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Chapter 6

Non-invasive diagnosis of urinary bladder outlet obstruction in patients with lower urinary tract symptoms using ultrasound decorrelation analysis. .

Based on the publication:

M. Arif, Jan Groen, Egbert R. Boeve, Tim Idzenga, Chris L. de Korte and Ron van Mastrigt, 'Non-invasive diagnosis of urinary bladder outlet obstruction in patients with lower urinary tract symptoms using ultrasound decorrelation analysis'. Accepted "The Journal of Urology" .

Abstract

Aims: To develop a non-invasive method for diagnosing Bladder Outlet Obstruction (BOO) in male patients with Lower Urinary Tract Symptoms (LUTS), sequential ultrasound images were successfully recorded during voiding in 45 patients.
Methods: Each patient voided in sitting position and ultrasound data were acquired transperineally.
Results: The results showed that the decorrelation (decrease in correlation) between subsequent ultrasound images was higher in bladder outlet obstructed patients than in the unobstructed patients and healthy volunteers. A linear relationship was fitted between the degree of obstruction represented by BOOI measured in separate pressure flow studies and the decorrelation values.
Conclusion: Receiver Operating Characteristic (ROC) analysis resulted in an area under the curve (AUC) of 0.96, proving that, it is possible to use the ultrasound decorrelation analysis technique to non-invasively diagnose BOO with an accuracy of 96%, a 95% specificity and 88% sensitivity.

1. Introduction

Benign prostatic enlargement often leads to Bladder Outlet Obstruction (BOO) in elderly men. Nocturia, low urinary flow rate, post-void dribbling and post-void residual volume are common symptoms of BOO. Urodynamic pressure-flow studies (PFS) are used as the standard procedure to diagnose BOO (1). A major disadvantage of this method is the urethral catheterization, which causes partial obstruction during micturition and may alter the diagnostic results. The invasive nature of the procedure also causes discomfort and pain to the patients and might result in infection. Therefore, the development of a non-invasive alternative method of diagnosing BOO is needed. A variety of non-invasive and more patient friendly diagnostic methods for BOO, such as the condom catheter method, the penile cuff method, perineal sound recording, ultrasonic measurement of bladder wall thickness and Doppler flowmetry (2-6) have been proposed. All of these techniques have some drawbacks and none of them has been applied routinely in clinical practice.

To develop an accurate clinical urodynamic method to diagnose BOO, we applied a non-invasive ultrasound (US) decorrelation based technique to quantify flow velocity and turbulence in silica gel urethra models (7, 8). This technique is based on comparing the scatter pattern in a group of images constructed from sequentially acquired ultrasound radiofrequency (RF) signals due to reflections from small scattering particles. If the particles move slowly the images will be similar, that is, they will be highly correlated. If the particles move fast, then the images will be less similar and the correlation will be less, that is, there will be a higher decorrelation. In urine various types of crystals such as calcium oxalate, uric acid and amorphous urates have been identified (9, 10). These crystalline structures can act as small ultrasound scattering particles. In a previous study (11) we showed that morning urine contains a sufficient concentration of these scattering materials to be suitable for US imaging of urinary flow using the decorrelation method. We subsequently tested and applied the method in healthy volunteers and defined a relation between decorrelation and urinary flow velocity (12). In a phantom with increasing severity of obstruction we found higher decorrelation values than in the unobstructed urethra models at the same flow velocity. This was due to turbulent flow as a result of an obstruction (8). On this basis we hypothesized that in patients suffering from BOO we could find higher decorrelation values than in the healthy volunteers at the same flow velocity and it might be possible to develop a practical method for noninvasively diagnosing BOO in male patients with lower urinary tract symptoms (LUTS). In the present study, we applied the decorrelation method in patients with LUTS to diagnose BOO and compared the results with conventional PFS.

2. Materials & Methods

2.1 Population

Following institutional research ethics board approval (MEC-2013-419), we recruited 60 male patients with LUTS, suggestive of BOO in the period January – October 2015. All patients gave their informed consent. Completing an International Prostate Symptom Score (IPSS) form to quantify their urological condition was part of routine practice.

2.2 Experimental setup

Each patient voided in a sitting position with an ultrasound transducer placed gently against the perineum using a specially designed chair with a mechanical transducer manipulator (Fig 1(A)). To adequately visualize the urethra, the transducer was manually moved in angular and sidewise directions by the investigator using the vertical handle (Figure 1(B)). To acquire RF US data of the urinary stream a BK-Medical system (Pro Focus UltraView 2202) with a custom designed RF interface was used. The acquired RF signals were stored on an external Personal Computer (PC) using a frame grabber (OR-X4 C0-SE-F00, Imago Group, Waalre, The Netherlands). The flow rate was measured with a rotating disk flow meter (Disa Electronics, Denmark) and stored on a PC using an Analogue/Digital (A/D) converter (PCI 6220, National Instruments, Austin, Texas, USA) in combination with a custom written LabVIEW program (National Instruments, Austin, Texas, USA). The US data acquisition was synchronized with the flow rate signal. The voided volume was measured at each voiding using a measuring jug.

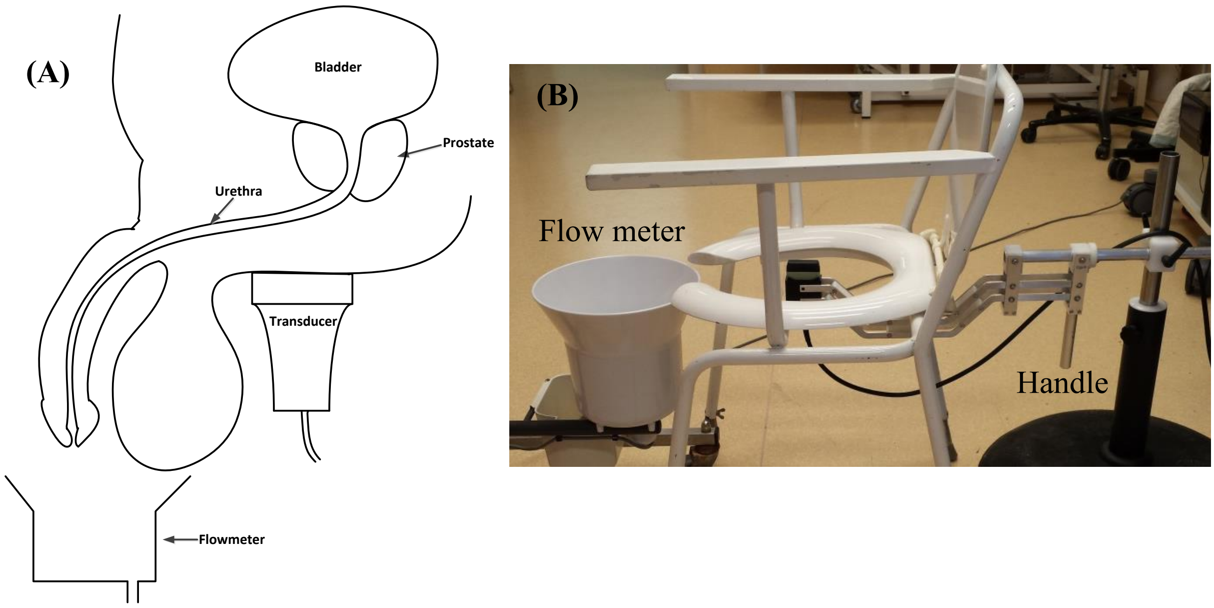

Figure 1: *(A) Schematic drawing and (B) picture of the experimental setup. The US transducer position was controlled by a specially designed manual probe manipulator.*

2.3 Data acquisition

From each patient we acquired four measurements. The 1st measurement was a free flow measurement, that is, a flow measurement without transurethral catheter, with US data acquisition. The following two were conventional invasive PFS done by the Andromeda urodynamic system (Medizinische Systeme GmbH, Potzdam Germany) without US data acquisition. Finally, the bladder of the patient was refilled with a saline solution. Since filling of bladder with saline results in urine with less scattering particles, therefore microbubbles, approximately 4x105 /litter (SonoVue, Braco International B.V. Amsterdam, the Netherlands), were added to this solution to enhanced the scattering particles reflection. The catheter was then removed and again a free flow measurement with US data acquisition was recorded. We acquired 5seconds of US data at a frame rate of 10 Hz. Each US frame contained 10 sequential RF data sets (images). Every RF data set consisted of 142 RF-signals acquired at a Pulse Repetition Frequency (PRF) of 0.5 kHz. Each RF-signal yielded a single image-line in an image. The US frames were stored on an external PC and analyzed using custom written programs (Matlab, The MathWorks, Natick, MA, USA) .

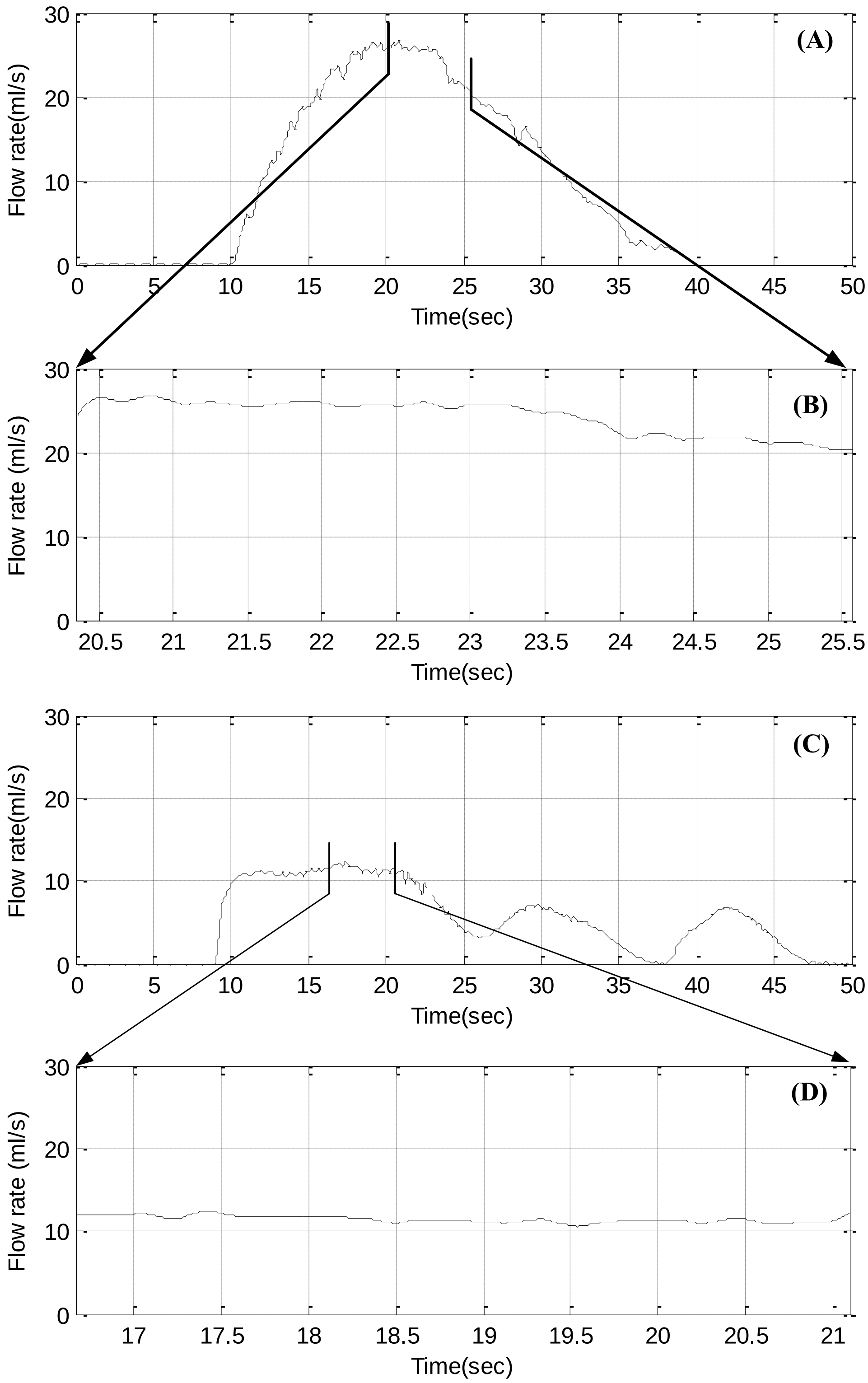

Figure 2: *A typical flow rate curve of a healthy volunteer (A & B) and an obstructed patient (C & D) as a function of time.*

2.4 Data analysis

2.4.1 ***Correlation coefficients:*** In each US frame we calculated the correlation coefficients (ρ) between the RF-data sets at a larger time interval (i.e. data sets 1 with 5, 2 with 6, 3 with 7 etc.). To do this, segments of data points from two RF lines representing a certain echo depth were taken and the correlation coefficients between these segments were calculated. This was repeated for all image lines of the full data-set and a correlation coefficient distribution (correlation image) was constructed by using a colour code for each correlation value (a more detailed description of the correlation coefficients calculation has been given in (7)). For each US frame, from 10 US RF-data sets, 6 correlation images were thus constructed. In order to calculate the mean values, a normal distribution of the correlation coefficients was realized by applying the Fisher Z-transformation (13). After transformation we calculated the mean $\bar{z}$ in a Region Of Interest (ROI). The position of the ROI (length 1.8 cm) was manually selected in each correlation image just distal to the prostatic urethra. The mean $\bar{z}$ then transformed it back to $\bar{\rho}$ by computing the inverse Fisher Z-transformation. Next we calculated the average (ρ_{avg}) of these $\bar{\rho}$ values over the 6 correlation images for each US frame.

As US frames were acquired at different flow rates during voiding in each patient, we calculated ρ_{avg} values at each of these flow rates and corresponding flow velocities. The flow velocity v (cm/s) in the urethra corresponding to a measured flow rate value Q (ml/s) was calculated using the relation, $v = Q/A$, where $A\,(cm^2)$ is the cross-sectional area of the urethra, which was calculated using the relation $A = \pi \left(\frac{D}{2}\right)^2$, where $D(cm)$ is the diameter of the urethra measured at the center of the ROI using the ultrasound system. The calculated average correlation values ρ_{avg} were plotted as a function of the flow velocity.

2.4.2 ***Relationship between decorrelation and degree of obstruction:*** To define a relationship between the decorrelation and the degree of obstruction we fitted a curve through the decorrelation and flow velocity data acquired in healthy volunteers using the relation:

$$\rho_{avg}(k) = a\,\{v(k)\}^b + c \qquad (1)$$

where a, b and c are constants and k = 18, is the number of volunteers (12). Next we calculated the differences between the correlation values of equation 1 and the patients correlation values at the same flow velocity (experimental quantification parameter of BOO). We plotted these as a function of Bladder Outlet Obstruction Index (BOOI), which was used as the gold standard quantification parameter for the degree of BOO (14). In each patient the BOOI, was calculated by the Andromeda urodynamic system (Medizinische Systeme GmbH, Potzdam Germany). A linear relation was fitted to the data:

$$\text{Corr diff} = d_1 * \text{BOOI} + d_2 \qquad (2)$$

where d_1 and d_2 are constants. From Equation 1, we subtracted the correlation difference calculated using equation 2 at BOOI values of 20 and 40, thus creating correlation-velocity boundary curves for these values in a correlation-velocity nomogram. We also calculated the Receiver Operating Characteristic (ROC) curve to test the diagnostic value of the method (see Figure 6). To this end, patients were stratified in two groups on the basis of invasive PFS. Patients with BOOI of 40 or less were labelled unobstructed (i.e. equivocal or unobstructed according to the standard BOOI nomogram) and those with higher BOOI were labelled obstructed. The area under the curve (AUC) shows the percentage of the patients that are correctly diagnosed by the method. The specificity and sensitivity of the decorrelation method were also calculated.

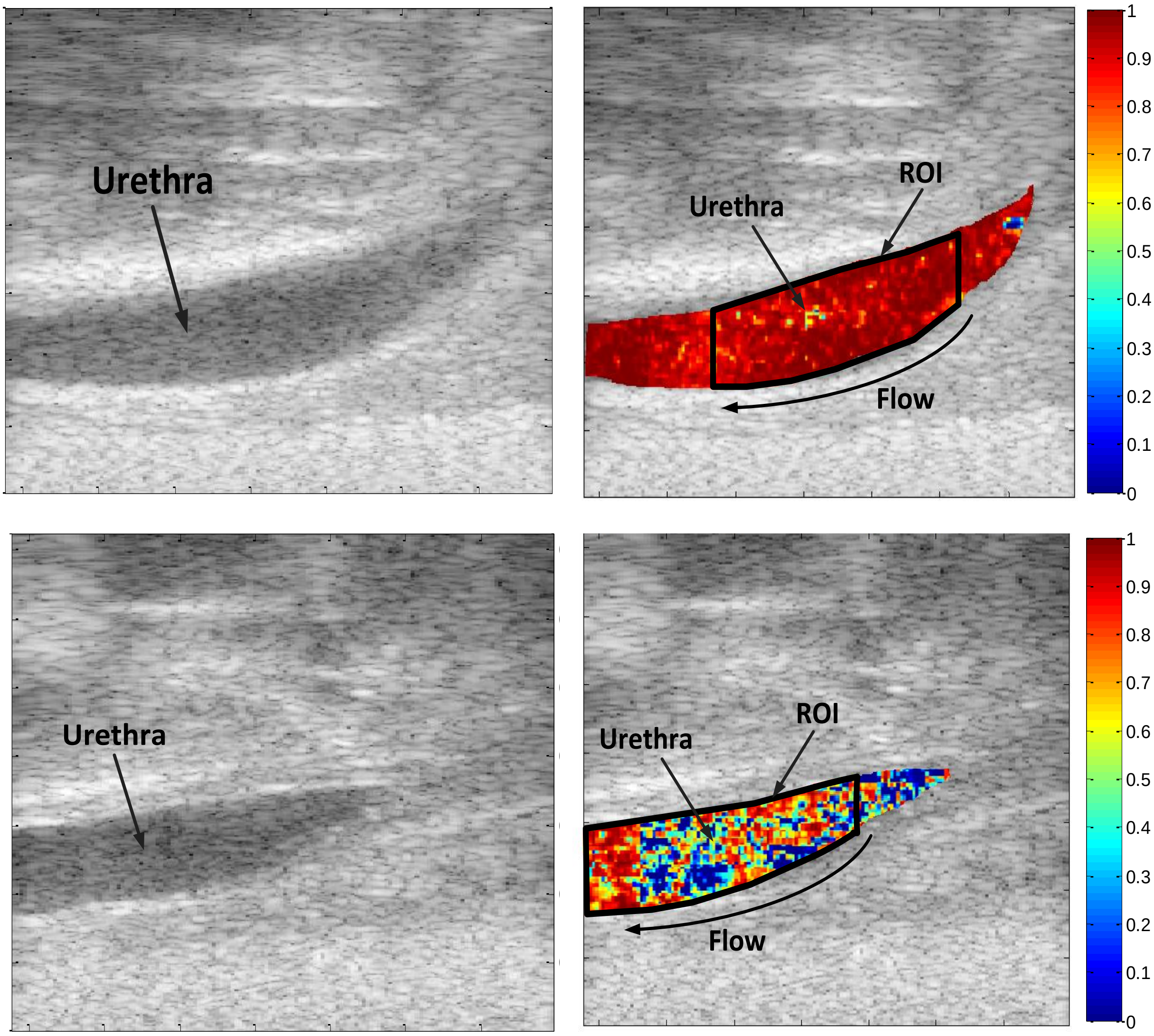

Figure 3: *(A) Example of in vivo US B-mode image and (B) Correlation coefficient distribution overlaid on the US B-mode image of the urethra during voiding of a healthy volunteer. (C) Example of in vivo US B-mode image and (D) Correlation coefficient distribution overlaid on the US B-mode image of the urethra during voiding of an obstructed patient (BOOI = 75). The Region of Interest (ROI) and the measured urethra diameter are also shown. 1 represents to high correlation and 0 to low correlation.*

3. Results

3.1 Population

We included 60 patients. Five patients were not able to void during the complete examination. From these 5 patients, 3 patients had an indwelling catheter. Five patients were not able to produce a free flow with the US transducer placed perineally and in 5 patients the

US data was not usable due to a wrong positioning of the transducer or due to movement of the patient during voiding. In the remaining 45 (75%) patients, at least one US urinary flow data was recorded. The voided volume, maximum free flow rate, age, IPSS and BOOI of these 45 patients are shown in Table 1. The pressure-flow nomogram of the patients is shown in Figure 4(B).

3.2 In-vivo Results

A typical urinary flow rate curve of a volunteer and a patient are shown in Figure 2(A) & 2(C). The flow rate values corresponding to the 50 acquired US frames are shown in Figure 2(B) & 2(D). An example of an in vivo US B-mode image of the urethra of a healthy volunteer and an obstructed patient during voiding is shown in Figure 3(A) & 3(C). The correlation images constructed from the 1st and 5th US RF-data set are overlaid on the B-mode images (see Figure 3(B) & 3(D)). The ROI distal to the prostatic urethra is also visible. A plot of the calculated ρ_{avg} values as a function of flow velocity for volunteers and patients is shown in Figure 4(A). The diagram shows that the correlation coefficients of the obstructed patients were lower than those of the healthy volunteers at the same flow velocity, that is, the decorrelation was higher in these patients.

3.3 Relationship between decorrelation and degree of obstruction

In Figure 5 (A), we plotted the difference in ρ_{avg} of patients and the model fitted to the healthy volunteers data as a function of BOOI. The difference between the correlation values increased with the degree of obstruction. The R-square value of the fitted linear model is 0.55 with constants d_1= 0.0041 and d_2= -0.074. In Figure 5(B), we constructed the nomogram to categorize the patients in different obstruction levels based on the US correlation data values. It illustrates that 86%, that is, 39 out of 45 patients could be classified correctly. In ROC analysis, an AUC value of 0.96 signified a diagnostic accuracy of 96% (See Figure 6). The specificity and sensitivity of the method were 95% and 88%.

4. Discussion

The standard procedure to diagnose BOO involves urethral catheterization which is uncomfortable to patients. The invasiveness of the method may also cause infections of the urinary tract. Therefore a non-invasive urodynamic method to diagnose BOO is desirable. In this study we applied US decorrelation analysis on patients with LUTS to diagnose BOO and compared the results with standard PFS.

In 45 out of 60 patients we successfully recorded the US urinary flow data. The principle finding of the study is that in patients with BOO the correlation values are decreased with respect to the healthy volunteers as shown in Figure 3 and Figure 4(A). The reason for this higher decorrelation could be that the narrowing in the urinary flow channel due to the urethral obstruction results in a disturbed (turbulent) urinary flow. The correlation difference plotted as a function of BOOI shows that the decorrelation is significantly correlated with BOOI. By measuring the decorrelation using US it might be possible to estimate BOOI in patients with voiding symptoms. Categorization of patients in different obstruction levels using BOOI is illustrated in Figure 5(B). In an ideal situation all the obstructed patients should have correlation values below the BOOI=40 curve, however the fitted relation to estimate BOOI from the decorrelation could be a source of error.

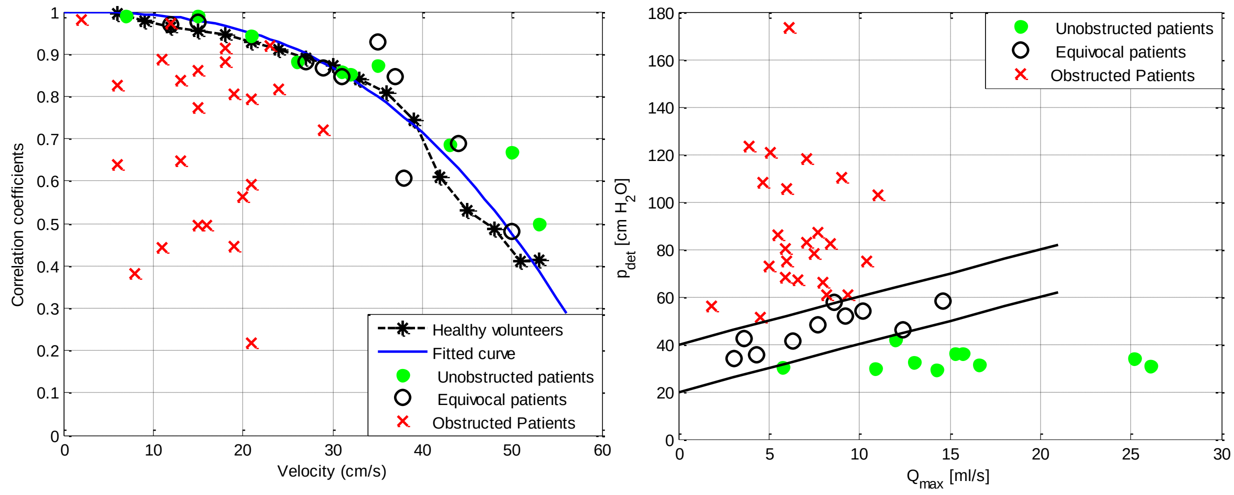

Figure 4: *(A) The calculated average correlation coefficients and fitted function of 18 healthy volunteers and correlation values of 45 patients plotted as a function flow velocity. (B) Classification of 45 patients based on pressure-flow study.*

In a previous study in healthy volunteers (12) US data during voiding were acquired in the standing position. In the present study patients urinary flow US data were acquired in the sitting position. In a meta-analysis De Jong et al. (15) no difference in urinary flow rate of healthy men in sitting or standing position was found. Therefore the correlation data of healthy volunteers in standing position can be compared to the data of the patients acquired in the sitting position. We preferred to do the measurement in the sitting position for patients, often elderly, as it was easier to void sitting while also preventing motion artefacts.

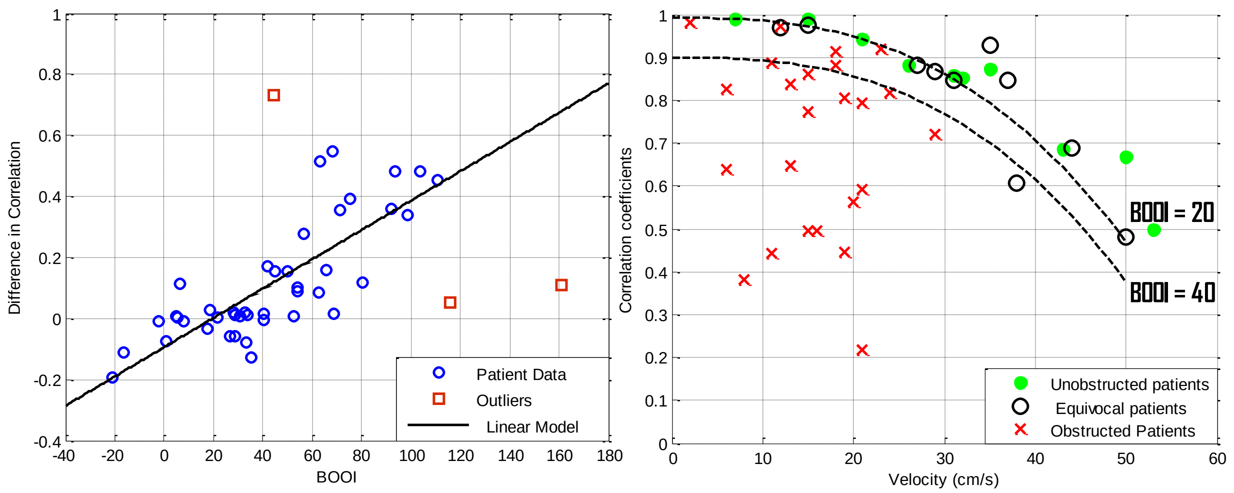

Figure 5: *(A) Difference in correlation between healthy subjects and patients plotted as a function of BOOI. (B) Correlation-velocity nomogram to diagnose BOO in LUTS patients.*

The advantage of pressure-flow study over the decorrelation method is that the bladder can be refilled and the diagnostic process can be repeated. In addition, with a catheter present, information on the storage phase of the micturition cycle can be obtained. In the non-invasive decorrelation method, patients are not catheterized and repeating the study can only be done after natural refilling of the bladder which takes time. Additionally, the decorrelation method depends on particle concentration (11). A high fluid intake with subsequent dilution of urine could therefore affect the results. Future studies should address this aspect of the

Table 1: Age, IPSS, voided urine volume (ml), maximum urinary flow rate (ml/s) and BOOI of the 45 patients in whom a successful measurement was done.

Patient	Age (years)	IPSS	Voided Urine Volume (ml)	Maximum Flow rate (ml/s)	BOOI
1	50	15	760	13	29
2	77	10	150	11	54
3	70	23	425	10	19
4	65	22	470	12	6
5	65	27	155	3	53
6	55	11	250	12	75
7	80	18	325	5	92
8	72	18	295	5	63
9	74	15	280	5	68
10	66	24	290	5	45
11	61	22	472	10	27
12	53	23	300	7	28
13	90	No	160	5	22
14	80	17	180	13	81
15	76	21	156	12	40
16	83	18	250	15	45
17	51	24	255	14	5
18	68	23	170	5	161
19	54	20	265	4	116
20	61	16	490	16	-21
21	59	18	220	13	72
22	70	13	200	13	5
23	64	10	290	13	33
24	74	10	170	5	54
25	64	No	220	5	99
26	78	14	200	14	69
27	68	18	260	10	42
28	77	33	250	10	18
29	59	19	30	11	-2
30	50	31	240	9	42
31	54	11	710	15	1
32	72	25	300	14	31
33	67	8	160	7	66
34	70	No	360	20	63
35	72	No	240	10	93
36	77	18	340	7	57
37	72	No	390	8	33
38	79	No	200	12	8
39	65	17	325	8	111
40	78	No	150	11	29
41	80	7	100	3	35
42	72	No	200	14	-16
43	51	No	175	6	34
44	65	No	300	5	104
45	67	No	230	8	50

No = IPSS of the patients were not recorded.

decorrelation method. However, these disadvantages are more than compensated by the non-invasive nature of the method.

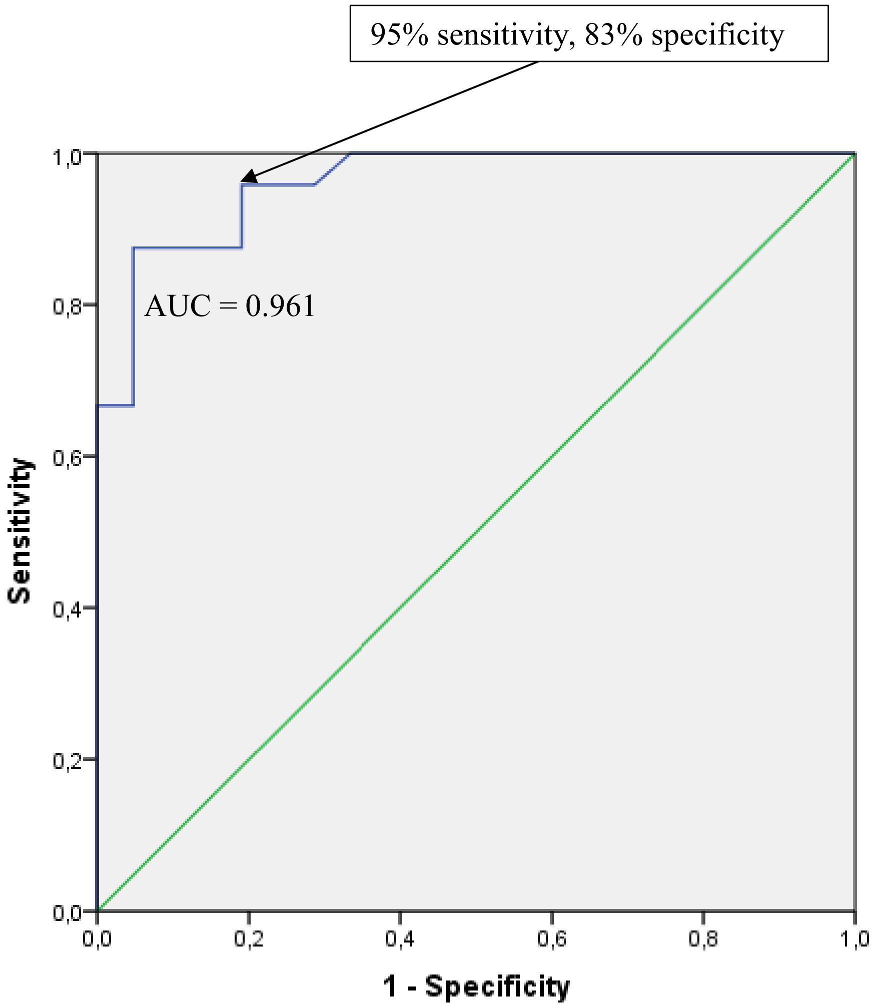

Figure 6: *Receiver Operating Characteristic curve (ROC) of the non-invasive decorrelation method with an area under the curve (AUC) of 0.96.*

5. Conclusion

Decorrelation based analysis of urinary flow US data showed that the decorrelation was higher in obstructed patients than in unobstructed patients and healthy volunteers at the same flow velocity. The relationship between BOOI and differences in correlation values of patients and the fitted curve of healthy volunteers showed that the degree of BOO can be non-invasively estimated using US decorrelation analysis and the measured correlation values can be used to diagnose BOO in male patients with high specificity (95%), sensitivity (88%) and a diagnostic accuracy of 96%.

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PART IV

GENERAL DISCUSSION

Chapter 7

Discussion, Conclusion and Summary

1. Discussion

Elderly men often develop Lower Urinary Tract Symptoms (LUTS), such as low urinary flow rate, frequent (nocturnal) voiding and incomplete emptying of the bladder, which significantly affects their daily life. The possible cause of these LUTS is either a weakly contracting bladder or Benign Prostate Enlargement (BPE) (1). Over fifty years of age, around 68% men have histological evidence of prostatic enlargement (2, 3). BPE can result in compression of the urethra and may lead to Bladder Outlet Obstruction (BOO). The standard urodynamic method to diagnose BOO is the pressure-flow study, which is invasive, time consuming and involves urethral catheterization (4). Several non-invasive and more patient friendly urodynamic methods have been proposed to diagnose BOO in patients with LUTS, such as the condom catheter method (5), the penile cuff method (6), perineal sound recording (7). However, as yet, these methods cannot adequately replace the standard invasive diagnostic method. Therefore, the development of a non-invasive but accurate urodynamic method of diagnosing BOO is needed.

In this thesis, we presented a new application of ultrasound (US) decorrelation analysis for a non-invasive diagnosis of BOO in patients. In the in-vitro part of the thesis, we applied this technique to quantify flow velocity and turbulence in urethra models. In part III of the thesis, this technique was applied in a group of healthy volunteers and in BOO patients.

1.1 Flow velocity Estimation

In fluid dynamics, according to the law of mass conservation ($Av = Q$), at a constant value of flow rate (Q) and cross-sectional area (A) along the tube, the flow velocity (v) remains constant. However, in the case of an obstruction in the tube , the cross-sectional area in the obstruction is decreased, which results in an increased flow velocity. A similar phenomenon can be found in BOO patients. Therefore, we hypothesized that the estimation of urinary flow velocity could be used to differentiate between healthy and obstructed patients.

Ozawa *et al.* (8) used color Doppler ultrasound to measure urinary flow velocity in the urethra. In a small patient population, they calculated the ratio of urine flow velocities measured in the distal prostatic urethra just above the external sphincter and in the sphincteric urethra and defined a velocity ratio cut-off point to diagnose BOO. However, high urinary flow velocities (up to 300cm/s) have been reported in the literature (9), and the effect of aliasing at such high flow velocities limits the use of color Doppler ultrasonography. A time-domain decorrelation analysis may provide an advantage in estimating these higher urine flow velocities without aliasing (10). In cardiology, this method has been used to estimate blood flow velocity in diseased (stenosis) arteries using intravascular ultrasound catheters (11, 12). The decorrelation method compares the scatter pattern of a group of images constructed from sequentially acquired ultrasound radiofrequency signals reflected by small scattering particles. If the particles move slowly the images will be similar i.e. highly correlated, so there is not much decorrelation (decrease in correlation). If the particles move fast, then the correlation between images quickly decreases and there will be a high level of decorrelation.

In chapter 2, we used this decorrelation analysis to estimate flow velocity in obstructed and unobstructed urethra models in three US beam zones: near field, focal zone and far field.

Results indicated that it is feasible to estimate flow velocities in a wide range (0–300 cm/s) in obstructed and unobstructed urethra models from the decorrelation of RF ultrasound signals.Because of the smaller beam width in the focal zone, the decorrelation was more rapid than in the near and far field. To estimate very high flow velocities (e.g., ≥ 800 cm/s), the beam width needs to be adjusted or measurements have to be performed in the far field, which is characterized by a lower decorrelation rate (13).

Generally, a flowing medium without particles does not reflect ultrasound signals (14). In blood flow imaging, blood cells act as the ultrasound scattering medium. As normal urine does not contain blood cells, it was thought that urine does not contain particles that scatter ultrasound signals. However, Elliot and Rabinowitz (15) and Verdesca *et al.* (16) identified different types of crystals in urine. Crystalline structures such as calcium oxalate, uric acid and amorphous urates were the most frequent (16). Calcium oxalate crystals occur in urine in the dihydrate and monohydrate format and account for 76% of all crystals. The monohydrate crystals range from 2 to 34 μm; the dihydrate crystals range from 2 to 104 μm (15). These crystals can act as scattering particles to reflect ultrasound signals. However, the concentration of these crystals in urine is not known and it can vary between and within patients. Furthermore, the particle concentration may have an effect on estimating the decorrelation of US signals. Therefore, in chapter 3 we studied the influence of particle concentration on the decorrelation of US signals in urethra models using both water with scattering particles and stepwise diluted urine from nine healthy volunteers. Results showed that the concentration of scattering particles does effect the estimation of decorrelation from sequentially acquired US images. The correlation increases with an increase in the concentration of scattering particles and generally morning urine contains sufficient scattering particles to be used for decorrelation imaging of urinary flow (17).

1.2 Relation between decorrelation and degree of obstruction

Accoding to the principles of fluid dynamics, the narrowing of a flow channel, can also result in a disturbed or turbulent flow. For laminar flow the change in the scatter pattern between sequential images is expected to be small and the correlation to be high. However, for turbulent flow the change between sequential images is expected to be large and the correlation to be lower. In cardiovascular research, decorrelation based flow estimation using US has been used to study the disturbance of flow in coronary arteries due to plaque formation. Bonnefous *et al* (18) showed that the variance in blood flow downstream of a stenosis in the carotid arteries increases and that the decorrelation of US signals could be used to estimate the increase of variance. Idzenga *et al* (19) also showed that audible sound produced by turbulence downstream of an obstruction in a urethra model is related to the degree of obstruction. We assumed that a higher degree of obstruction creates more turbulence in the urinary flow, which could result in a higher decorrelation. To test this hypothesis, we did an experimental study to relate decorrelation information to different degrees of obstruction in the urethra models as described in chapter 4. We found that the the decorrelation between sequential US images increased with an increasing degree of obstruction. Therefore, the quantification of decorrelation between sequential US images could be a new technique to noninvasively diagnose BOO (20, 21).

1.3 Non-invasive diagnosis of BOO

In humans, the anatomical properties of the obstruction and the viscoelastic properties of urethra may vary and could influence the decorrelation analysis results. Therefore, after the urethra model study, a clinical study was first conducted on the applicability of the non-invasive US decorrelation method in healthy male volunteers to acquire baseline measurments in healthy subjects for interpretation of results in patients. Also it was necessary to test the method in healthy volunteers first in order to develope a complete procedure and device for imaging the urinary tract in patients. We investigated the variability in decorrelation values between and within healthy volunteers at maximal and submaximal values of flow rate and flow velocity. The results showed that the correlation had no unique relationship with flow rate, but it decreased uniquely with increasing flow velocity. Li (11) reported that in an arterial model, the decorrelation directly related to the displacement of particles and, thus, to velocity. For a constant cross-sectional area (A) flow velocity increases with an increase in flow rate (10) and thus causes an increase in decorrelation. However, because of the viscoelastic properties of the urethra, the cross-sectional area of the urethra may also increase with an increase in flow rate and may cause the flow velocity to decrease, remain constant or increase slightly. Therefore, the relation between decorrelation and flow rate is not as strong as that between decorrelation and flow velocity (22). We also found that the variation in measurements within volunteers was significantly smaller than the variation in measurements between the volunteers. This showed that based on decorrelation analysis the volunteers can be distiguished.

Following the good results in the healthy volunteers, a clinical study in patients with Lower Urinary Tract Symptoms (LUTS) was necessary in order to establish the diagnostic value using the decorrelation method. Therefore, we conducted a clinical study on the applicability of the non-invasive US decorrelation method in patients and compared the results with standard pressure flow studies. Following institutional research ethics board approval (MEC-2013-419), we recruited 60 male patients with early symptoms of BOO. The results showed that the decorrelation values in patients with BOO were higher than the healthy subjects and unobstructed patients at the same flow velocity. The reason for this higher decorrelation is that the narrowing in the urinary flow channel due to the urethral obstruction results in a disturbed (presumably turbulent) urinary flow. The plot of the BOOI and the difference in correlation values of healthy subjects and patients showed that the decorrelation increases with the degree of obstruction. Therefore, by measuring decorrelation value, it may be possible to estimate BOOI in a patient with LUTS. We also plotted a correlation-velocity nomogram to categorize the patients in an obstructed and an unobstructed group. The comparison of the correlation-velocity nomogram with the pressure-flow studies nomogram showed a good agreement. Almost all obstructed patients have correlation values under the curve represented by BOOI=20. Whereas the unobstructed and equivocal patients have correlation values above or on the curve.

1.4 Advantages and limitation of the US decorrelation method for diagnosing BOO

In the field of urodynamic, the non-invasive US decorrelation method has some advantages and some limitations compared to other non-invasive techniques and the standard invasive urodynamic method. The major advantage of the decorrelation method over the standard pressure-flow study is its noninvasive nature. Additionally, the data acquisition is faster than the standard method as it does not involve urethral catheterization and bladder filling which is part of the procedure of a standard pressure flow study. Another advantage is that this method also does not require an interruption of urinary flow during voiding as required by some other non-invasive techniques such as condom-catheter (5) and the penile cuff method (6).

The decorrelation method to diagnose BOO can be compared to Doppler flowmetry (23). In Doppler video urodynamic, urinary flow velocity was also measured, but due to turbulence and high urinary flow velocity aliasing can occur and limit the use of color Doppler US. In Doppler, Continues Wave (CW) and Pulsed Wave (PW) methods are used. Continuous Wave (CW) Doppler could be used to avoid aliasing and measure high urinary flow velocity, but depth (spatial) information is not available in this technique. In PW Doppler, spatial information can be acquired but at very high flow velocities and/or in the presence of turbulent flow, aliasing can occur. Whereas in the decorrelation based analysis of US signals the urinary velocity can be measured in a wide range (up to 300cm/s) (13).

A major limitation of our method is that the bladder of the patients cannot be filled with saline solution containing scattering particles and decorrelation analysis cannot be performed without voiding. The study can be done after natural filling of the bladder by drinking a sufficient amount of water. However, this is time consuming. Additionally, the decorrelation analysis depends on the concentration of scattering particles in urine (17) and larger fluid intake can dilute the urine more, which in turn could affect the results. Out of plane imaging of the urethra during voiding is another issue of the study. To successfully acquire US data of urinary flow, the transducer position against the perineum is very important. Furthermore, patient motion during voiding could also cause poor data acquisition. The latter two limitations could be solved by using 3D US imaging and computing decorrelation in three directions. The method also requires expensive US equipment to acquire US data of the urinary flow.

Most of the non-invasive and standard invasive diagnostic methods do not measure the location of the obstruction in the urethra. Also the decorrelation method only gives an indication of the presence of BOO. A detailed assessment of the location of the obstruction might be possible using US strain imaging. At the location of the obstruction strain is higher than in the other parts of the urinary tract. During voiding, the radial pressure increases in the urethral tissue which induces strain in the prostatic urethra. US data could be acquired before and after compression and using cross-correlation of images before and after the compression, the strain in different parts of urethra can be calculated and the variation in the degree of resistance of the urethra along its length could be estimated.

1.5 Future perspective

Our promising results show that decorrelation based analysis of US data could be used to clinically diagnose BOO. However the method needs to be validated in a larger population with more optimized and more easily controllable equipment. The general practitioner/technician needs to be trained to get good image/US data during voiding. A real time programming of the decorrelation analysis could make the technique more readily and easily applicable. Decorrelation analysis using 3D imaging might give the exact location of the obstruction in the urinary tract.

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2. Conclusion

In this thesis, we implemented the decorrelation method of US radiofrequency signals of urinary flow data to non-invasively diagnose BOO. The results of the urethra model and clinical studies suggest that BOO can be diagnosed using this US decorrelation based analysis. The comparison of our results with pressure-flow studies showed that most of the obstructed patients are also categorized obstructed according to decorrelation analysis

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Summary

Elderly men often develop Lower Urinary Tract Symptoms (LUTS), such as incomplete emptying of the bladder, weak urinary stream and frequent voiding. A weakly contracting bladder or an enlarged prostate resulting in Bladder Outlet Obstruction (BOO) can also lead to such symptoms. Over the age of fifty years, 68% men have histological evidence of benign prostatic enlargement. The standard method to diagnose BOO is a pressure flow study which involves urethral catheterization. Based on measured urinary flow rate and pressures values in bladder, the method categorizes the patients in obstructed, unobstructed or equivocal groups using a pressure-flow nomogram. This method is time-consuming and uncomfortable to the patients. A variety of non-invasive and more patient-friendly methods have been proposed to diagnose BOO in patients with LUTS. However, as yet, these methods are not applicable in clinics.

In this thesis, we investigated decorrelation (a decrease in corrleation between sequential ultrasound signals) based analysis of Ultrasound (US) signals of urinary flow data to non-invasively diagnose BOO. The work of the thesis is devided into two parts. Part I deals with urethra model studies to provide a base for further in-vivo analysis. Part II describes the results of the cilinical studies done in healthy volunteers and in patients with LUTS. **Chapter 1** gives an overview of the standard invasive method and the different existing non-invasive methods to diagnose BOO. The aim and outline of the thesis are also described in details.

In **Chapter 2**, we implemented the decorrelation based analysis on US radiofrequency signals to estimate urinary flow velocity in soft tissue mimicking urethra models. It is shown that the relation between decorrelation and urinary flow velocities can be used to estimate a wide range (≤ 300 cm/s) of flow velocities, which can be expected in case of obstruction.

In **Chapter 3**, we investigated the effect of different concentrations of particles in urine on the decorrelation analysis of US signals. As urine dilution can change with fluid intake, the change in the decorrelation of ultrasound signals in urethra models using both water with scattering particles and stepwise diluted urine from healthy volunteers was studied. The results showed that the decorrelation values change with the particle concentration and that morning urine is most suitable for the acquisition of urinary flow data.

Chapter 4 describes the relation between the decorrelation and different obstruction levels. We used four urethra models with different degrees of obstruction and found that the correlation values decreased approximately linearly with an increase in degree of obstruction. This was probably due to an increase in turbulence level just after the obstruction in the urethra models.

In **Chapter 5**, we applied the decorrelation method to healthy male volunteers. The study was carried out in 20 healthy male subjects. Each volunteer voided in a standing position and US data was acquired during free flow. The results indicated that the decrease in correlation (decorrelation) of ultrasound radiofrequency signals had no unique relation with flow rate, but decreased uniquely with urinary flow velocity. We also found that the variation in measurements between healthy subjects was statistically significant.

In **Chapter 6**, we describe a clinical study in which we applied the decorrelation based analysis to non-invasively diagnose BOO in 60 male patients with LUTS. It was shown that

the decorrelation method could be used to estimate the Bladder Outlet Obstruction Index (BOOI) in patients. A correlation-velocity nomogram was developed to categorize the patients as obstructed or unobstructed.

Chapter 7 describes the merits of the decorrelation method and provides the advantages and disadvantages as compared to standard method and the conclusion of the thesis.

Samenvatting

Oudere mannen krijgen vaak last van plasproblemen (LUTS) zoals het niet geheel legen van de blaas, een zwakke urine stroom en vaak moeten plassen. Een slecht werkende blaasspier of een vergote prostaat met als resultaat een blaasuitgangsobstructie (BOO) kunnen beiden de oorzaak zijn van de plasproblemen. Ongeveer 68% van de mannen ouder dan vijftig hebben histologische aanwijzingen van een goedaardige prostaatvergroting. De standaard gebruikte methode voor het diagnosticeren van BOO is een druk-flow onderzoek, hierbij wordt een catheter in de blaas gebracht via de plasbuis. Daarmee wordt de druk in de blaas gemeten samen met de urinestroom. Met behulp van dit onderzoek studie kan een patient gediagnosticeerd worden als geobstrueerd, niet-geobstrueerd of er tussen in. Dit wordt gedaan met een druk-flow nomogram. Deze methode is echter zeer tijdsintensief en oncomfortabel voor de patient. Een scala aan niet-invasieve en patient vriendelijkere methoden voor het diagnosticeren van BOO in patienten met plasproblemen zijn in de loop der tijd geopperd. Geen van deze methoden is echter nog grootschalig geimplementeerd in de kliniek.

In dit proefschrift heb ik een niet-invasieve diagnose techniek voor BOO die is gebaseerd op de decorrelatie tussen opeenvolgende ultrageluid opnamen. Deze decorrelatie is een afname van de correlatie tussen opeenvolgende ultrasound signalen. Het onderzoek is in dit proefschrift beschreven in twee gedeelten. Deel I behandelt de model studies die de basis vormen voor de verdere *in-vivo* analyse. Deel II beschrijft de resultaten van *in-vivo* studies in een populatie van gezonde vrijwilligers en in een populatie van patienten met LUTS. **Hoofdstuk 1** geeft een overzicht van de standaard invasieve druk-flow diagnose methode en de verschillende alternatieve niet-invasieve technieken voor het diagnosticeren van BOO. Hierin staan ook de doelstelling en de outline van het proefschrift beschreven.

In **Hoofdstuk 2** heb ik de op correlatie gebaseerde analyse van ruwe ultrageluid signalen onderzocht in een model studie. In modellen met eigenschappen die vergelijkbaar zijn met de plasbuis heb ik op basis van de correlatie van opeenvolgende ultrageluid opnamen de stroomsnelheid geschat. Deze studie toonde aan dat op basis van deze correlatie analyse een breed scala aan realistische stroomsnelheden in het geval van BOO (tot 300 cm/s) geschat kan worden.

In **Hoofdstuk 3** heb ik het effect onderzocht van verschillende concentraties van deeltjes in urine op de decorrelatie analyse. Hiervoor heb ik de decorrelatie onderzocht van ultrageluid signalen van water en urine stromend door urethrale modellen. Urine werd verzameld van een aantal vrijwilligers. Omdat de concentratie van deeltjes in de urine kan veranderen door drinken, bevatte het water verschillende concentraties van deeltjes en werd de urine van de vrijwilligers in verschillende stappen verdund. De resultaten lieten zien dat de correlatie van de ultrageluid signalen afhankelijk was van de concentratie van de deeltjes. Ochtendurine was het meest geschikt voor de decorrelatie analyse.

Hoofdstuk 4 beschrijft de relatie tussen de correlatie van ultrageluid opnamen en de mate van obstructie in de plasbuis. In vier plasbuis modellen met verschillende maten van obstructie vond ik dat de correlatie tussen opeenvolgende ultrageluid opnamen bij benadering lineair daalde (decorrelatie) met een toename in obstructie. Een mogelijke verklaring hiervoor is een toename van turbulentie in de stroming stroomafwaarts van de obstructie.

In **Hoofdstuk 5** heb ik de decorrelatie methode toegepast in een populatie van 20 gezonde mannelijke vrijwilligers. Iedere vrijwilligers plaste in staande positie en gedurende het plassen werd de ultrageluid data ter hoogte van het perineum geregistreerd. De resultaten vertoonden geen unieke relatie tussen de decorrelatie van opeenvolgende ultrageluid opnamen en de volumestroom. Er was echter wel een unieke positieve relatie tussen de decorrelatie en de stroomsnelheid. Een andere bevinding was dat de decorrelatie in de metingen significant verschillend was tussen de gezonde vrijwilligers.

In **Hoofdstuk 6** wordt een klinische studie beschreven waarin ik de decorrelatie methode toegepast heb in een populatie van 60 mannelijke patienten met LUTS. Deze studie toonde aan dat de decorrelatie van ultrageluid een mogelijk alternatief kan zijn voor het standaard druk-flow onderzoek voor het diagnosticeren van BOO in patienten met LUTS. In dit hoofdstuk is ook een decorrelatie-stroomsnelheid nomogram ontwikkeld voor het diagnosticeren van patienten als geobstrueerd of niet-geobstrueerd.

Hoofdstuk 7 beschrijft de waarde van de decorrelatie methode en de voor- en nadelen van deze methode in vergelijking met de standaard druk-flow test. Tevens omvat dit hoofdstuk de conclusies.

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Publications

Journal Papers

- **Arif M**, Idzenga T, van Mastrigt R, de Korte CL. 'Estimation of Urinary Flow Velocity in Models of Obstructed and Unobstructed Urethras by Decorrelation of Ultrasound Radiofrequency Signals'. Ultrasound Med Biol. 2014 Jan 9:938-46.

- **Arif M**, Idzenga T, de Korte CL, van Mastrigt R. 'Dependence of ultrasound decorrelation on urine scatter particle concentration for a non-invasive diagnosis of bladder outlet obstruction. Neurourol Urodynam'. 34(8), p 781 – 6, 2015.

- **Arif M**, Idzenga T, de Korte CL, van Mastrigt R. 'Development of a Noninvasive Method to Diagnose Bladder Outlet Obstruction Based on Decorrelation of Sequential Ultrasound Images'. Urology. 2015;85(3):648-52.

- **Arif M**, van Mastrigt R, Idzenga T, de Korte CL. 'Diagnosing bladder outlet obstruction using non-invasive decorrelation based ultrasound imaging: A feasibility study in healthy male volunteers'. Ultrasound in Med. & Biol Vol. 41, No. 12, pp. 3163–3171, 2015.

- Idzenga T, **Arif M**, de Korte C, van Mastrigt R. 'Noninvasive estimation of the pressure profile in the male urethra using ultrasound imaging', 42(4), p 1745 – 52, 2015.

- **Arif M**, Groen J, Boevé RE, Idzenga T, de Korte CL, van Mastrigt R. 'Non-invasive diagnosis of urinary bladder outlet obstruction in patients with lower urinary tract symptoms using ultrasound decorrelation analysis'. Accepted '*The Journal of Urology'* (In press).

Conference Proceedings, Abstracts, Posters and Talks

- **Arif M**, Idzenga T, van Mastrigt R, de Korte CL. A Correlation-based Ultrasound Method for the diagnosis of Bladder Outlet Obstruction. International Continence Society (ICS), 2012 beijing China.

- Van Straten M, **Arif M**, Van Mastrigt R. Can Bladder Outlet Obstruction Be Diagnosed from the Urethral Cross-Sectional Area Estimated by Ultrasound Imaging? Neurourol Urodynam. 2012 Aug;31(6):841-3

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- **Arif M**, Idzenga T, de Korte CL, van Mastrigt R. Decorrelation of Ultrasound Rf-Signals for a Non-Invasive Diagnosis of Bladder Outlet Obstruction. Neurourol Urodynam. 2013 Aug;32(6):752-4.

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- **Arif M**, van Mastrigt R, Idzenga T, de Korte CL. Dependence of ultrasound decorrelation on urine scatter particle concentration. Ultrasonics Symposium (IUS), 2014 IEEE International; 2014 3-6 Sept. 2014.

- **Arif M**, Idzenga T, de Korte CL, van Mastrigt R. Diagnosing bladder outlet obstruction using non-invasive decorrelation based ultrasound imaging: A feasibility study in healthy male volunteers’. ICS Annual meeting 2015, Montreal, Canada.

Curriculum Vitae

Muhammad Arif was born in Gujranwalla, a splendid city in Pakistan, on August 4 1982. He received his undegraduate degree in physics from the University of Punjab, Lahore, Pakistan in 2004. In the same year he started to work in a private company in Lahore, Pakistan. In 2007, he moved to Stockholm Sweden and started a Master study in Medical Imaging at the Royal Institute of Technology (KTH). For this study he worked at the Radiology department of the Linkoping University Hospital, Linkoping Sweden,

In 2011 he joined the Deparment of Urology, Sector Furore at the Erasmus Medical Center in Rotterdam, The Netherlands as a PhD student under the supervison of Prof. dr.ir. Ron van Mastrigt. His PhD project was a joint research project between the Department of Urology of Erasmus MC Rotterdam and the Medical Ultrasound Imaging Centre, department of Radiology, Radboud University Nijmegen Medical Centre. During his PhD he focused on the development of a non-invasive ultrasonic diagnosis of urinary bladder outlet obstruction. The result of his research have been presented on various international scientific meetings and published in peer reviewed journals.

PhD Portfolio

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PhD training		
General and Specific courses	Year	ECTS
Dutch language course Beginners level (A1)	2012	1.0
Dutch language course Pre-Intermediate (A2.1)	2012	1.0
English Biomedical writing and communication	2014	3.0
Biostatistical Methods I: Basic Principles (CC02)	2014	5.7
Seminars and workshops		
Basic to Advanced Clinical Urodynamics (workshop)	2012	1.0
Basic Urodynamics - an interactive workshop (workshop)	2012	1.0
Presentations		
STW Project meeting/ presentation, Erasmus MC	2012	1.0
STW Project meeting/ presentation, Erasmus MC	2013	1.0
Research meeting at department of Radiology, Nijmegen MC, Netherlands	2013	1.0
STW Project meeting/ presentation, Erasmus MC	2014	1.0
STW Project meeting/ presentation, Erasmus MC	2015	1.0
International conferences		
International Continence Society (ICS), Beijing China	2012	
• *Poster presentation*		1.4
• *Oral and poster presentation*		2.0
International Continence Society (ICS), Barcelona Spain	2013	
• *Oral and poster presentation*		2.0
IEEE International Ultrasonics Symposium (IUS), Chicago USA	2014	
• *Poster presentation*		1.4
International Continence Society (ICS), Montreal Canada	2015	
• *Short Oral presentation*		2.0
Total		26.5