Continence 1 (2022) 100008

Contents lists available at ScienceDirect

Continence

journal homepage: www.elsevier.com/locate/cont

Development and initial testing of valves opened by Valsalva (abdominal straining): Proof of principle for urinary catheters or male urethra

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ARTICLE INFO

Keywords:
Catheter valve
Stent
Abdominal straining
Incontinence
Urethral catheter

ABSTRACT

We hypothesised that raising the abdominal pressure could provide a non-manual approach to opening a urinary valve, with potential application for indwelling catheters or an intraurethral device. The 'Vysera' valve remains closed during short high amplitude spikes but opens when a pre-defined low-amplitude pressure is maintained for a pre-specified duration, allowing sustained abdominal straining to achieve voluntary opening. The valve was subjected to in vitro performance and microbiological tests. Parameters for valve specification were selected by review of a large urodynamic database with nominal opening pressure of 75 cmH_2O +/−15 cmH_2O (range 60–90 cmH_2O) and valve pressure was refined using early clinical results. Valve housings were designed for the end of a Foley catheter, and for male post-prostatectomy intraurethral placement. Preliminary clinical evaluation was undertaken for both designs, incorporating qualitative feedback. In vitro testing of the catheter valve demonstrated only minimal encrustation. On clinical evaluation of the catheter-sited valve, six of seven patients (86%) were able to open the valve intentionally by straining. When inactive, none of the patients experienced leakage (7/7 = 100%), while five (71%) leaked when they coughed. The intraurethral device was successfully placed with image intensifier guidance under general anaesthetic in five of nine patients. Three patients used the device; initial leakage resolved as patients mobilised. However, in contrast to the catheter-sited valve, the intraurethral device was difficult to tolerate for even a few hours. Removal was performed under local anaesthesia with a flexible cystoscope and stent grasper. We conclude that storage and bladder emptying using a strain-activated valve are feasible for a catheter valve and an intra-urethral device. The valve parameters need to be matched to individual patients. For the intraurethral device, additional development is needed to improve the stent housing and valve performance.

1. Introduction

Urinary catheter valves are commonly used with indwelling catheters (IDC) to provide an alternative to collection of urine in a bag. This is preferred by many patients, and can reduce time to blockage for the catheter [1]. However, some IDC users are unable to use a valve due to various reasons, such as impairment of their manual dexterity [2]. Hence an alternative valve design could increase the number of people able to use a valve with their IDC. We hypothesised that raising the abdominal pressure could serve as an alternative valve opening mechanism. This would require the valve to have suitable properties allowing intentional opening by Valsalva manoeuvre (prolonged deliberate increase in abdominal pressure), but minimising the risk of unintentional opening by abdominal pressure fluctuations associated with ordinary physical activity.

Use of abdominal straining to open the valve means that manual dexterity is not needed to use the valve, and access to the valve may not be needed in everyday use. This extends the potential application of the valve for entirely intraurethral use, using a suitably-designed valve housing to prevent valve displacement and also prevent incontinence. This could increase patient choice by providing an alternative to an IDC, and may reduce some of the problems associated with IDC use, such as catheter-associated urinary tract infection (UTI) and catheter blockages.

A valve that opens by increasing abdominal pressure must be able to;

- Stay closed (continent) during the storage phase
- Withstand abdominal pressure generated by routine activity, such as lifting or sneezing.

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https://doi.org/10.1016/j.cont.2022.100008

- Allow opening for voiding, at a time chosen by the patient
- Close again once the bladder has emptied.

We surmised that abdominal pressure during routine activity is generally of short duration and substantially below the maximum potential straining amplitude, particularly in people with limited physical strength. We also considered that patients may be able to initiate higher amplitude and more sustained contractions by voluntary Valsalva manoeuvre, in excess of the typical pressures seen during normal activity.

The 'Vysera' valve is a proprietary one-way valve which can be manufactured to remain closed until a pre-defined hydrostatic pressure is maintained for a pre-specified duration. Thus, appropriately selected parameters would mean that even high amplitude abdominal pressure change (as in powerful coughing) would not open the valve, since the duration would be too short. In contrast, the more sustained pressure elevation for opening could be set to a modest level, to enable valve opening by Valsalva at a time the patient desires.

To test the principle of a valve that can be opened by Valsalva, we made a valve using specifications developed from a urodynamic database review and direct measurements from IDCs. To evaluate potential to use it as an IDC valve, we housed it in a casing to fit into a standard catheter, for pilot tests in patients. We then adapted the parameters of the valve to suit use in an intraurethral location, where it could be held by a specially-designed stent. This was designed for the male urethra, for patients who had previously undergone radical prostatectomy (RP) and had post-prostatectomy incontinence (PPI).

This report describes the development work for the Vysera valve, the stent housings (catheter and intraurethral), and the deployment mechanism required to correctly place the valve in the male urethra. We then describe findings of the first in human clinical studies, undertaken to test key performance requirements of a valve;

1. The ability of patients to open the valve in the two locations (IDC or intraurethral)
2. Ability of clinicians to place a valve in the male urethra and remove it
3. Valve performance (storage, bladder emptying, closure and tolerability).

For use as an intraurethral device, the valve also required a suitable deployment mechanism and adequate housing ("stent") for it to remain in place at the RP vesico-urethral anastomosis. The following stipulations were proposed:

- Stent-mounted valve must be compressible, in order to fit within a 21Fr sheath for deployment
- Once deployed, the stent configuration needs to prevent proximal (into bladder) and distal (along urethra) migration
- The stent should be removable with a conventional flexible cystoscope from any location (the intended site at the vesico-urethral anastomosis, or incorrectly/ displaced location)

2. Materials and methods

2.1. Design

2.1.1. Valve design

The Vysera valve uses a polymer-based material configured with a deformable outer ring (which absorbs short duration pressure spikes) and a trifoliate spiral centre which "unwinds" during sustained pressure to open the lumen (Fig. 1). The valve is compressible and returns to its original shape on relief of compression, making it feasible to place in a tube for intracorporal deployment. The duration needed to open the valve is modified by altering the physical characteristics of the outer ring and the unwinding spiral. The opening amplitude is altered through the physical stiffness of the polymer. The lumen closes when the valve resets automatically (approximately 15 s after cessation of flow). Valves can specify opening pressures between 20 and 350 cmH_2O, requiring an applied duration of 5–10 s.

2.1.2. Identifying required valve specifications

The likely ranges of pressures that could be encountered *in vivo* at rest, and during coughs and strains, were measured from a large urodynamic database collated from a tertiary referral centre [3]. In brief, the ranges of vesical pressures encountered during strains and during coughs were measured from 200 consecutive urodynamic traces. The results were used to specify the range of pressure response characteristics of the valve.

2.1.3. Valve housing

The Vysera valve was designed with two types of housing. For use with IDC, it was placed into a polycarbonate housing for attachment directly to the external end of a Foley catheter (Fig. 2).

For use as an intraurethral valve, a stent housing and a suitable deployment system were required to allow correct positioning in men with RP. A silicone coated nitinol stent was selected due to shape-memory properties, allowing recovery of shape after being compressed into the deployment system. The configuration of the deployed stent was designed to retain the valve at the intended site (Fig. 3); the funnel-shaped proximal part of the stent sat at the vesico-urethral anastomosis, to avoid distal migration. The bulbous part (configured for the urethral bulb) aimed to counteract any movement in the opposite direction (proximal migration).

2.1.4. Intraurethral valve deployment and removal

The valve–stent construct was inserted and deployed by a 21Fr delivery system consisting of an angled hydrophilic polyurethane outer sheath and an inner pusher shaft. This delivery system was advanced to locate the valve at the vesico-urethral anastomosis. The initial attempt to do this without fluoroscopy led to mis-sited deployment, so imaging was employed for subsequent procedures. The stent was deployed by holding it in place with the pusher whilst withdrawing the sheath.

For removal, the 21Fr sheath was placed over a flexible cystoscope and advanced to the distal end of the stent under direct vision. Ureteric stent graspers were passed along the biopsy channel of the cystoscope and used to draw the stent and valve back into the sheath (slowly, to give time for the materials to configure to the smaller space), before withdrawing the cystoscope and sheath (enclosing retrieved valve and stent housing) together.

2.2. Pre-clinical testing

2.2.1. Conformity to specification

For testing of performance against specification, the valves were placed in a polycarbonate housing with a friction-grip end suited to a Foley catheter. The catheter proximal end was placed within a pressurised vessel containing water at 37 °C. The pressure within the vessel was controlled with an electronic pressure regulator (SMC Pneumatics ITV1010-311BL5-X323) driven with a customised signal generator (Vysera), capable of generating steady state and dynamic pressure patterns between 5 and 70 cmH_2O and with impulse and rise times between 0.1 s and 99.99 s (resolution of 0.01 s). Applied pressure was measured using an electronic transducer (Sensortechnics SSIM700GU9AH5) located adjacent to the device.

2.2.2. Microbiological performance

In-vitro studies in a laboratory model of the catheterised bladder were undertaken, to investigate the time to blockage of the Vysera valve in comparison to the 'Flip-Flo' valve (Bard Ltd). The valves were placed in an in-vitro glass bladder model previously described by Stickler et al. [1,4]. In brief, it consists of a glass chamber (the bladder) maintained at 37 °C by a water jacket. Each model was sterilised by autoclaving and then a size 14Ch Latex Romed catheter (provided by Vysera) was inserted into the bladder chamber through a section of silicone tubing (the "urethra") at the base of the model. Catheters were secured in place at the outlet of the bladder model by inflation of

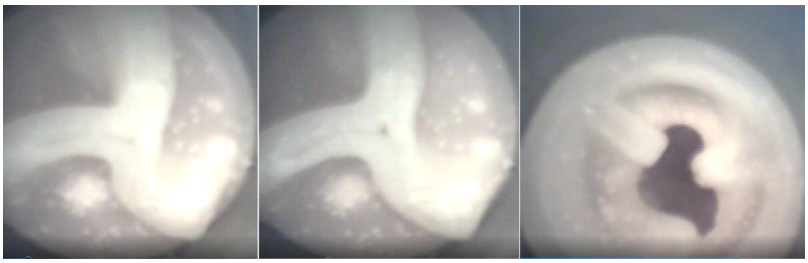

Fig. 1. Endoscopic view of a Vysera valve *in-vitro*. **Left:** Vysera valve in its closed configuration, illustrating the radial trifoliate arrangement. **Centre:** During a modelled cough pressure spike, the outer valve leaflets are pushed away from the endoscope. **Right:** During a modelled Valsalva sustained above threshold for sufficient duration, the radial elements straighten and separate to give an open channel for emptying.

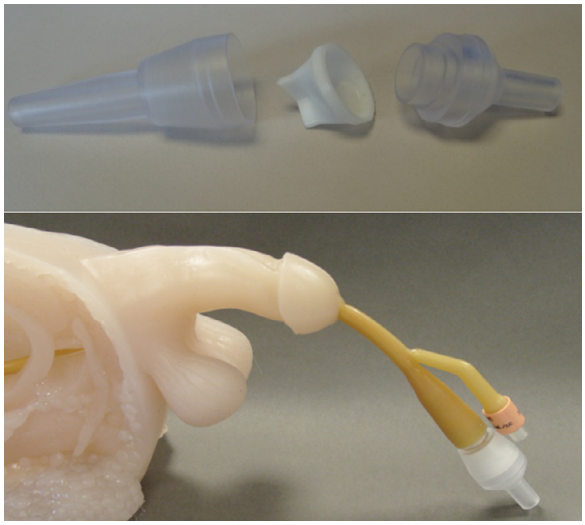

Fig. 2. Catheter (external) version of the valve. **Top image**; the valve and the polycarbonate housing disassembled. **Lower image**; assembled device placed into the distal end of a standard Foley catheter.

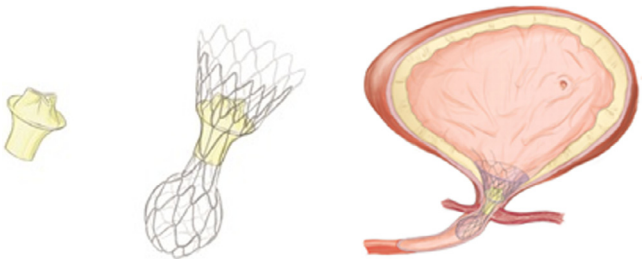

Fig. 3. Vysera valve schematics. **Left:** the Vysera valve without its housing. **Centre:** the nitinol housing demonstrating the proximal funnel to prevent distal migration, and the bulbous element to prevent proximal migration. **Right:** the intended location of the device in situ, in a male with PPI.

their balloons with 10 ml of deionised water. The ends of the catheters were then attached to either a Vysera valve, Flip-Flo valve, or left open for continuous drainage. Sterile artificial urine was pumped into the chambers and exited via the IDC.

Standard inocula (10 ml of a 4-hr culture in artificial urine) of P. mirabilis NSM6 was introduced into the bladder chamber of the models. The test strain is a clinical isolate from an encrusted catheter, capable of generating alkaline urine and crystalline biofilm. After 1 hr incubation to allow the cultures to establish themselves in the models, the artificial urine was supplied to the models at 0.5 ml/min. The number of viable bacteria was determined at the start of the experiment. The time taken for the catheters to block was recorded. Three replicates of each experiment were completed.

For the Vysera Valve, an automated opening and closing protocol was initiated at four hourly intervals (SyringePumpPro software Version 2.2), activating a pump to depress a 100 ml syringe (to open the valve), wait 4 min (to allow drainage) and then withdraw (to close valve). For the Flip-Flo Valve, the valve was opened and closed manually at 8am, 12pm, 4pm and 8pm, switching to continuous drainage overnight. An automated system was also developed for Flip-flo opening at four hourly intervals with no period of continuous drainage.

2.3. Clinical testing

Both the prototype Vysera valve and the intraurethral deployment system were manufactured and sterile packaged to clinical standards, with approval of the UK Medicines and Healthcare Regulatory Agency (MHRA). The UK West Midlands–South Birmingham Research Ethics Service gave ethical approval for a two-stage proof-of-principle study, first testing the effectiveness of the Vysera valve in a catheter (NRES reference number 10/H1207/94) and second its capabilities as an intra-urethral device (NRES reference number 14/WM/1064).

2.3.1. Strain-activated catheter valve

Seven ambulant patients with chronic indwelling urethral catheters were recruited, after informed consent, to a proof-of-principle study. For testing, the housed valve was placed in the external end of the patient's indwelling Foley catheter. A drainage bag was connected to the distal end of the valve to capture any leakage through the valve during physical activity. The patients undertook a programme of changes in position (including lying to sitting, and sitting to standing), ambulation and coughs of increasing strength. At least two filling cycles (natural filling) and voids (strain-initiated) were undertaken for each patient. The valve specifications were individually selected to tolerate cough and strain pressures that it was empirically estimated that each patient could generate.

2.3.2. Intra-urethral stent-mounted valve placement, use and removal

Nine males with a history of RP were recruited after informed consent for the proof-of-principle study testing the intra-urethral valve device. The clinician (one senior urologist) completed a case report proforma which included information about the ease of device deployment, its positioning, and the ease of removal at the end of the study. The patients recorded the symptoms they experienced and how comfortable they were post-procedure. Where applicable, they reported their success with using the device and their general thoughts on its potential.

Four patients were recruited, after informed consent, to test the insertion and removal of the valve under general anaesthesia, in order to evaluate the feasibility of insertion, deployment and removal of the valve, in the context of RP anatomy. Device placement was undertaken under general anaesthesia and image intensifier fluoroscopy guidance, using the angled 21F hydrophilic sheath and a flexible cystoscope. Device removal was undertaken during the same anaesthetic, with the flexible cystoscope.

Table 1
Time to blockage of catheter with Vysera valve and two Flip-Flo valve protocols versus continuous drainage catheter.

	Time to blockage (hours)			
Model	Run 1	Run 2	Run 3	Mean time to blockage ±SE
Vysera Valve	92.0	125.1	125.1	110.4 ± 9.7
Continuous drainage	22.3	24.0	22.3	22.9 ± 0.6
Flip-Flo (automated)	44.1	38.2	53.1	45.1 ± 4.3
Flip-Flo (manual)	46.1	32.8	45.1	40.0 ± 3.9
Continuous drainage	21.7	19.0	24.1	21.6 ± 1.5

The remaining five patients were recruited, after informed consent, to have the valve placed under general anaesthesia. They were then woken from anaesthesia with the device in situ, to assess the valve. Upon recovery, the patients were all ambulant and undertook a programme of activity, including changes in position, ambulation and cough, as well as attempted voiding. The device was intended to remain in place so that enough time had elapsed for the patient to attempt to void using the device, where possible, on at least two occasions. Device removal was undertaken with the patient awake, employing the flexible cystoscope.

3. Results

3.1. Valve design and specifications

Analysis of the urodynamics database looked at the effect on vesical pressure of static (resting) and dynamic forces, to anticipate pressures the valves might encounter in a patient population. Resting vesical pressures of up to 44 cmH_2O were seen for sustained durations in the standing position. Pressure spikes during coughing of up to 76 cmH_2O above resting vesical pressure were found, with duration of up to 0.5 s. The median value of the maximal strain pressure during Valsalva was 75 cmH_2O (range 20–178 cmH_2O). The opening pressure specification for the valve to open was initially set at 75 cmH_2O +/-15 cmH_2O (range 60–90 cmH_2O). The valves were specified to remain shut at pressures of 20% above the opening pressures (“cough withstand factor”), where duration was less than 0.5 s, and with an interval of at least 0.5 s between successive coughs. These values were used for the intraurethral valves. An additional allowance was used in the IDC valves in recognition of the physical height difference caused by the lower location of the external end of an IDC compared to the vesico-urethral anastomosis. The specifications finally selected were a high opening pressure (up to 230 cmH_2O) and a cough withstand factor of 40%–70%.

3.2. Preclinical testing

3.2.1. Conformity to specification

The valves passed in-house quality assurance before release to patients.

3.2.2. Microbiological performance

Times to blockage in the *in vitro* bladder model inoculated with *Proteus mirabilis* are reported in Table 1. In all three runs for the Vysera valve there was very little crystal formation on the Vysera valve itself; the blockages occurred below the eyehole of the catheter.

3.3. Clinical testing

3.3.1. Catheter valve

The valve housing seated in the IDC without displacement. While inactive during the storage phase, none of the patients experienced leakage (7/7=100%). Five patients (5/7=71%) leaked when they coughed. Of these five, two only leaked when the cough was very aggressive (described as a ‘choking’ cough). On movement from changing positions from lying to sitting/ sitting to standing, or moving positions whilst lying or sitting, two patients (2/7=28%) experienced leakage.

Six of the seven patients (86%) were able to open the catheter-sited valve intentionally by straining. The one patient who could not had multiple sclerosis (MS) and was only physically able to generate a low-amplitude short-duration strain (maximum 65 cmH_2O for no more than 6 s).

Minor discomfort was reported by one patient. There were no complications. Patient comments included an opinion that the device was ‘brilliant’ as it could be operated ‘hands-free’. One patient raised concerns over the potential for leakage during the night.

3.3.2. Intra-urethral stent-mounted valve placement, use and removal

Four patients underwent insertion and removal of the stent-mounted valve under general anaesthesia, so the clinician could test the functionality of deployment system and removal process. During the first attempt (before fluoroscopy was employed), the device was wrongly deployed into the bladder; it was easily removed, and then correctly sited at the second attempt. Two (50%) patients underwent a successful device insertion and removal as planned (Fig. 4). In one patient the delivery system failed and could not be deployed, so the procedure was abandoned. Patients noted minor urethral discomfort only after the procedure, in keeping with undergoing a cystoscopy, with no change in their lower urinary tract symptoms.

Five patients were admitted to have the device inserted under general anaesthetic, after which they were awoken from anaesthetic to test tolerability and function of the device. It was then removed under local anaesthesia between three and five hours after placement, using a flexible cystoscope and ureteric stent grasper. Three (60%) of these patients underwent a successful device placement and were able to void successfully with the device in situ. One patient was found to have a urethral stricture at cystoscopy and thus the procedure was abandoned. The remaining patient had difficult urethral anatomy relating to his previous RP; the device could not be placed in the appropriate position, so it was removed while still under general anaesthesia.

All three patients noted some leakage with the valve in situ immediately post-anaesthesia. Once ambulant, the valve was continent during bladder filling (natural filling). The device remained in place during voiding, with voided volumes of 350 ml, 395 ml and 975 ml for the three patients, and complete bladder emptying as assessed by transabdominal bladder scan. The main difficulty was with patient tolerance, all three patients complaining strongly of penile tip pain. One patient also found the removal of the device under local anaesthetic particularly uncomfortable.

4. Discussion

The clinical study was a phase 1 first-in-human proof of principle to assess straining (Valsalva) as a means of valve opening. It looked at the functionality and tolerability of the Vysera valve when placed in either IDC or intra-urethral locations. It opened when pressure change above a predetermined threshold was sustained for sufficient duration. This was possible for six of the seven people using an IDC valve, and the three men who had an intraurethral stent-mounted valve. Thus, straining as a way to initiate valve opening is feasible, based on a small number of people. One person was unable to open it, due to weakness of their abdominal muscles limiting the strength of their Valsalva strain.

The valve stayed closed during brief pressure changes of high amplitude. This offered protection from many of the intra-abdominal pressure changes of short duration physical activities, such as coughing. The effectiveness with which the valve stayed closed appeared to be better for the intraurethral stent-mounted valve. After waking from anaesthesia, the three men using that type of valve did experience bypassing of the valve, which soon stopped. We speculate that this may have meant that the stent needed to settle into position, with the funnel properly against the RP vesico-urethral anastomosis to prevent

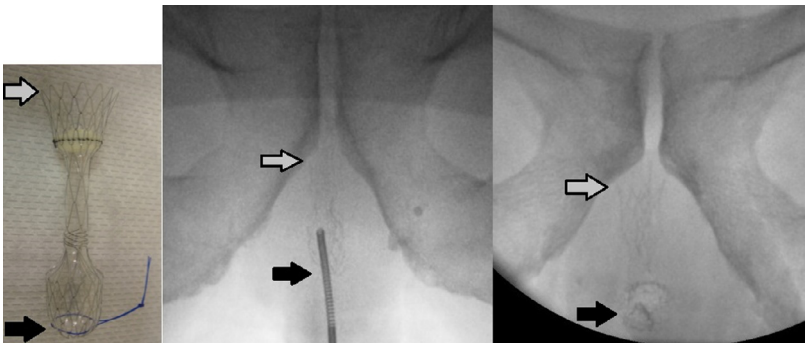

Fig. 4. Intraurethral valve in nitinol intraurethral stent housing. **Left image:** device before placement — open arrow indicates proximal end, closed arrow distal end. **Middle image:** device in situ seen with image intensifier during deployment — the coiled wire is part of the deployment system. **Right image:** another patient with the valve and stent fully deployed. In this patient, the distal component is seen end-on, due to the anterior angulation of the bulbar urethra.

urine bypassing the valve. The IDC valve was overcome by severe coughing for some people; we surmise that this was a result either of the sustained rise in abdominal pressure associated with a sequence of strong coughs, or it was due to the increased pressure changes seen at the external end of the IDC. Either way, the difference in abdominal pressure effects between intentional Valsalva and many physical activities may not be sufficient to be able to set valve parameters that reliably prevent the valve from opening during the latter.

In the preclinical laboratory testing, the valve performed according to manufactured pressure specifications. Microbiological challenge in vitro evaluated times to blockage with Vysera or Flip-flo valves, but the small sample size prevented formal comparison. Supply of Vysera valves was constrained by manufacturing capacity.

The concept of intraurethral valve systems have been reported for women [5,6], but were not well-tolerated and prone to technical problems. Likewise, the experience applying the principle in the male urethra identified a high chance that discomfort could preclude long-term use. The anatomy and complications post RP represents an additional challenge, preventing placement in two cases.

Initial valve specifications were generated from a large urodynamic database and refined based on early clinical testing, most importantly following recognition that pressures at the external end of the Foley catheter are higher than the intravesical pressures at symphysis pubis level identified from the urodynamics database, due to the extra hydrostatic pressure caused by the lower vertical height of the end of the catheter. The valve specifications (opening pressure) and cough withstand factors accordingly were different for the two sites of use. The pressures encountered during coughs and strains not only vary between patients, but a given patient generates a wide variety of pressures depending upon position, the nature of the stress event and the effort made to strain. For some patients, the effort possible is very limited. Each valve must therefore be chosen specifically for each patient after pressure variations have been assessed using urodynamic studies. Difficulty generating adequate intra-abdominal pressure would preclude use of this approach.

Considering the Vysera device firstly as an external catheter valve, it was felt that the device could potentially be useful for patients with limited manual dexterity or strength, for example secondary to osteoarthritis or MS, in place of the manual catheter valve. The patient would open the valve by a sustained period of abdominal straining at a socially convenient moment. Most patients were able to open the Vysera external catheter valve and achieve near-complete bladder emptying. Patients were able to open the valve by straining, unless they had considerable physical weakness, with advanced MS being a key causative factor in this study. The valve generally remained closed during rest and ambulation. It sometimes was forced open during severe coughing series. Once placed in its specific housing, the device was reliably retained in the end of a Foley catheter, and not displaced by altered intra-abdominal pressure. The valve was well tolerated, and most patients found the concept and reality of use straightforward. There were no complications with short term testing.

In the second stage of the study, the concept was adapted for intra-urethral use. The valve was placed into a specially designed stent so that it could be deployed and retained effectively at the vesico-urethral anastomosis in men with refractory PPI. The Vysera valve needed specific housing to hold it in position, and the ability to compress during deployment and removal, as well as retaining all the features required of it as a catheter valve. This stage of the study found that the deployment and removal systems for the device were comparatively straightforward to use. On the one occasion where the device was wrongly deployed into the bladder, it was easily removed. The clinician commented that graduated markings on the deployment catheter would aid placement, and fluoroscopy was also needed to determine location and ensure deployment at the intended location.

The main success of this aspect of the study was that three patients were able to utilise the device effectively, by successfully voiding to completion via the device after initiating abdominal straining. The device remained appropriately positioned until removal. Generally, the three patients who did test the device found it reasonably intuitive with good potential for future use. The two main issues that need to be addressed are patient comfort and the occurrence of urethral leakage despite the valve. Two of the patients found it difficult to tolerate the stent, even for the comparatively short duration of observation, and found its removal under local anaesthesia painful. It is hypothesised that penile tip pain was related to the nitinol stent component distending the bulbar urethra. Clearly the valve needs optimisation if it is to be effective, while the stent housing needs design adaptation to be tolerable in the longer term; it is proposed that the shape and radial force of the bulbar urethra component of the stent needs to be reviewed.

5. Conclusions

Urine storage and bladder emptying using a strain-activated valve are feasible, both as a catheter valve and as an intra-urethral device. In clinical practice, the valve parameters need to be matched to individual patients and their range of abdominal pressures. For the intraurethral device, additional development is needed to improve the stent housing and valve performance before considering clinical testing for longer term use.

Ethics approval and consent to participate

The UK West Midlands–South Birmingham Research Ethics Service gave ethical approval for a two-stage proof-of-principle study, first testing the effectiveness of the Vysera valve in a catheter (NRES reference number 10/H1207/94) and second its capabilities as an intra-urethral device (NRES reference number 14/WM/1064)

Funding

Funding for this proof-of principle research project was provided by Vysera Medical.

CRediT authorship contribution statement

Jennifer Martin: Writing – original draft. **Donal Devery:** Conceived the original idea and supplied the Vysera valve. **Michael Timothy:** Conceived the original idea and supplied the Vysera valve. **Andrew Gammie:** Design and perform the experiments to guide valve manufacture. **Nicola Morris:** Design and perform the experiments to guide valve manufacture. **Marcus J. Drake:** Design and conducted the clinicalVysera valve testing.

Acknowledgements

We are grateful to Ms Sophie Parke & Ms Hanne Jansen whose expertise greatly assisted this research. All authors approved the version of the manuscript to be published.

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