

Magnetically Controlled Endourethral Artificial Urinary Sphincter

T. MAZZOCCHI,¹ LEONARDO RICOTTI,¹ N. PINZI,² and A. MENCIASSI¹

¹The BioRobotics Institute, Scuola Superiore Sant'Anna, Viale Rinaldo Piaggio, 34, 56025 Pontedera, PI, Italy; and ²Urology Department, University of Siena, Via Banchi di Sotto, 55, 53100 Siena, Italy

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Abstract—Urinary incontinence is a largely spread dysfunction that affects more than 300 million people worldwide. At present, no technological solutions are able to restore continence in a minimally invasive and effective way. In this article the authors report the design, fabrication, and testing of a novel artificial endourethral urinary sphincter able to fully restore continence. The device can be inserted/retracted in a minimally invasive fashion without hospital admission, does not alter the body scheme and can be applied to both women and men. The device core is a unidirectional polymeric valve and a magnetically activated system able to modulate its opening pressure. Bench tests and *ex vivo* tests on a human cadaver demonstrated that the device is able to fully restore continence and to allow urination when desired. Overall, the proposed system shows a high potential as a technological solution able to restore a normal daily life in patients affected by urinary incontinence.

Keywords—Urinary incontinence, Artificial sphincter, Magnetic device, Minimally invasive therapy, Unidirectional valve.

INTRODUCTION

Urinary incontinence (UI) is a dysfunction that implies an involuntary leakage of urine and that affects more than 300 million people worldwide.¹⁵ UI mainly consists of an involuntary loss of urine following an increase of intravesical pressure (IVP). This may occur in correspondence to events such as coughing, laughing, sneezing, or physical exercise and it is mainly due to a deficient action of the urethral sphincter muscles.^{35,38}

In women, the main UI risk factors are highly correlated to age, pregnancy, childbirth, menopause,

hysterectomy, obesity, and other altered conditions. In men, the main UI risk factors are surgery procedures (e.g., prostatectomy) which alter the muscle structures of the pelvic floor and the urethral sphincter.^{4,20} For both men and women, the prevalence of UI increases with age. Indeed, important changes occur overtime in the bladder and in the pelvic structures, which contribute to UI inception.^{8,23,26}

The currently adopted solutions to overcome UI drawbacks can be classified into two categories: conservative and non-conservative ones.¹⁹ The most common conservative solution consists of sanitary napkins used to absorb a moderate amount of urine. This solution is cumbersome and requires frequent monitoring of the absorbent conditions, with obvious drawbacks in terms of patients' quality of life and psychological burdens. Another conservative solution consists of drug treatments. For example, antimuscarinic drugs aim at reducing undesired bladder smooth muscle contractions.¹ Hormonal treatments are also used to counteract muscular atrophy in women undergoing menopause.^{31,35} Finally, in some cases, UI can be faced by means of exercises for the pelvic floor muscles.³⁴

When the UI drawbacks are particularly severe, the aforementioned solutions become ineffective. In such cases, UI must be managed in a more invasive way. Some solutions need surgical procedures to be inserted and aim at restoring continence by modulating the human anatomy. Medical slings, for example, modulate the relative position of bladder and urethra.^{14,29} Other solutions are based on the surgical installation of a device around the urethra in order to perform a circumferential compression, thus restoring urine control (extraurethral devices). Examples of commercial devices based on this working principle are the ProAct system (Uromedica, Plymouth, USA), the ARTUSTM system (NanoPowers SA, Laussane,

Address correspondence to Leonardo Ricotti, The BioRobotics Institute, Scuola Superiore Sant'Anna, Viale Rinaldo Piaggio, 34, 56025 Pontedera, PI, Italy. Electronic mail: leonardo.ricotti@santannapisa.it, l.ricotti@sssup.it

Switzerland), the Zephyr ZSI 375 system (Mayor Group, Villeurbanne, France) and the AMS 800 system (American Medical Systems, Minnetonka, USA).^{2,6,7,27,37} In particular, the AMS 800 is considered the gold standard product for UI management and has been implanted in more than 150,000 patients, so far.²⁸ All the mentioned systems are featured by a high invasiveness due to their surgical implantation, with consequent hospital admissions. Moreover, complications due to device failure in the first year after device installation, urethral injury (tissue atrophy and erosion), infections, and generation of a high IVP during urination, occur with a relatively high frequency.⁹

Recent research efforts focused on reducing some of the mentioned drawbacks, by developing evolved extra-urethral devices. In order to minimize urethral injury, Lamraoui *et al.* designed a pneumatically actuated system able to dynamically manage the urethra compression. Pressure levels were adjusted depending on patients' physical activities, which were recognized by means of accelerometers.¹⁸ More recently, Ramesh *et al.* designed a wirelessly controlled extraurethral device equipped with ionic electro-active polymers. A suitable urethra compression and a real-time monitoring of the pressure exerted allowed to maintain continence.³⁰ This device would allow urination management in a simple way, through a wireless trigger. A similar system, although pneumatically activated, was proposed by Hached *et al.*¹³ Despite interesting results, the mentioned prototypes are still affected by the typical drawbacks of extraurethral systems, i.e., (i) high invasiveness of the installation procedure; (ii) urethral tissue injury (although reduced in comparison with the AMS 800, thanks to the variable pressure exerted); (iii) possible infections; (iv) non-physiological IVPs during urination and (v) need of invasive surgical procedures for device maintenance/replacement.

Endourethral devices (systems inserted in the internal urethra lumen) are featured by a significantly smaller invasiveness. The simplest systems that belong to this category are catheters, which drain the urine from the bladder and transfer it into an external bag, e.g., fixed to a patient's leg. This solution implies obvious practical limitations and significant psychological burdens for incontinent patients. Few more effective endourethral commercial systems exist. One of them is the Femsoft system (Rochester Medical Corp., Stewartville, USA),¹⁰ a device for the treatment of SUI in women that consists of a soft silicone catheter. One (internal) extremity of the system has a balloon shape, which allows to enlarge the urethra tissue thus blocking the urine flux and restoring continence. The other (external) extremity has a soft fun-

nel that allows an easy manual removal of the device, once the patient needs to urinate. Another interesting device is the InFlow (Vesiflo, NE Redmond, USA) system. It is an electromagnetic apparatus manageable *via* a battery-powered remotely control device positioned on the body surface. Its remote trigger allows an inner pump (stably positioned in the urethra) to pump urine out of the bladder. However, this device is not used for managing UI, but aims at facing incomplete bladder emptying due to impaired detrusor contractility.⁵

By analyzing the mentioned endourethral solutions, different drawbacks can be identified. At present, a unisex solution installable/removable with minimally invasive procedures is not available. In addition, existing solutions are not fully disappearing (with the word "disappearing" we mean a device that can be installed into the urethral lumen without any parts of the system that remain visible outside of the body after the installation, thus able to not alter the patient's body scheme).

In this work we report a novel magnetically-controlled endourethral artificial sphincter (AS) provided with a series of key features, namely: (i) it is fully disappearing in the body; (ii) its insertion is quick and painless and can be carried out through endoluminal procedures and without hospital admission; (iii) it guarantees continence in everyday life even when sudden abdominal muscle contractions and physical activity occur; (iv) it allows an easy urination management, when required; and (v) it has a unisex design that can be applied to both men and women. To the best of our knowledge, this device is the only existing solution for UI cumulating all such desirable features.

MATERIALS AND METHODS

Overall System Architecture

The AS for addressing UI described in this paper was based on a magnetic activation system, used as a trigger to allow urination when desired. Without such trigger, the AS was designed to fully guarantee continence. The AS was thought as a solution adaptable to both male and female anatomies. Its size allowed an easy positioning/removal, by exploiting common tools used in urology, without hospital admission. A fully disappearing solution was targeted: once installed, the device should remain completely inside the body, without any externally visible parts. Figure 1 depicts the concept and the different phases envisioned for the application of the targeted AS: the device is expected to be delivered into the urethra with an endoluminal procedure, using a suitable cannula and a spindle, and

to be removed by exploiting the reverse procedure used for its positioning. Video S1 also describes the whole concept.

More precisely, the device insertion procedure is expected to be based on the following phases: (1) insertion of a rigid cannula (a standard tool for cystoscopic analyses with rigid metal walls and a void internal volume) into the urethra; (2) pushing of the cannula inside the urethra, until reaching the bladder lumen; (3) insertion of the AS into the cannula; (4) pushing of the AS inside the cannula by means of another rigid tool, named pusher, until the AS reaches the bladder lumen; (5) retraction of both pusher and cannula, leaving the AS in position within the urethra.

Medical/Anatomical Constraints for System and Component Design

The devised installation/removal procedures for the AS are minimally invasive and would not require hospital admission. This implies that standard urological tools should be used, such as cannulas for cystoscopy (external diameter: 8 mm, internal diameter: 7.40 mm, length: 300 mm). This led to set the AS

external diameter at 7.25 mm. The device length was established based on both male and female anatomical constraints. To this aim, Computed Tomography (TC) scans across the sagittal plane of both male and female urinary system were acquired. This, together with information derived from anatomical atlas,²⁴ allowed to identify a suitable device length allowing the system to be comfortable and fully disappearing within the patient's body. Figure S1 shows two TC images, representative for male and female anatomies. In males, a device featured by a length of ~40 mm would satisfy the mentioned requirements, whilst in female subjects this value is reduced down to ~30 mm. Therefore, the more restrictive features of female anatomy brought to set the device length at 30 mm.

Anatomical constraints also served to identify the most advantageous external magnet positioning to obtain an effective trigger of the internal device. In fact, as described in the next section, the device operating principle was based on the interaction between a magnet embedded in the device (internal magnet) and another one to be positioned on the subject skin (external magnet), to start urination. To minimize the volume and thus the bulkiness of the external magnet,

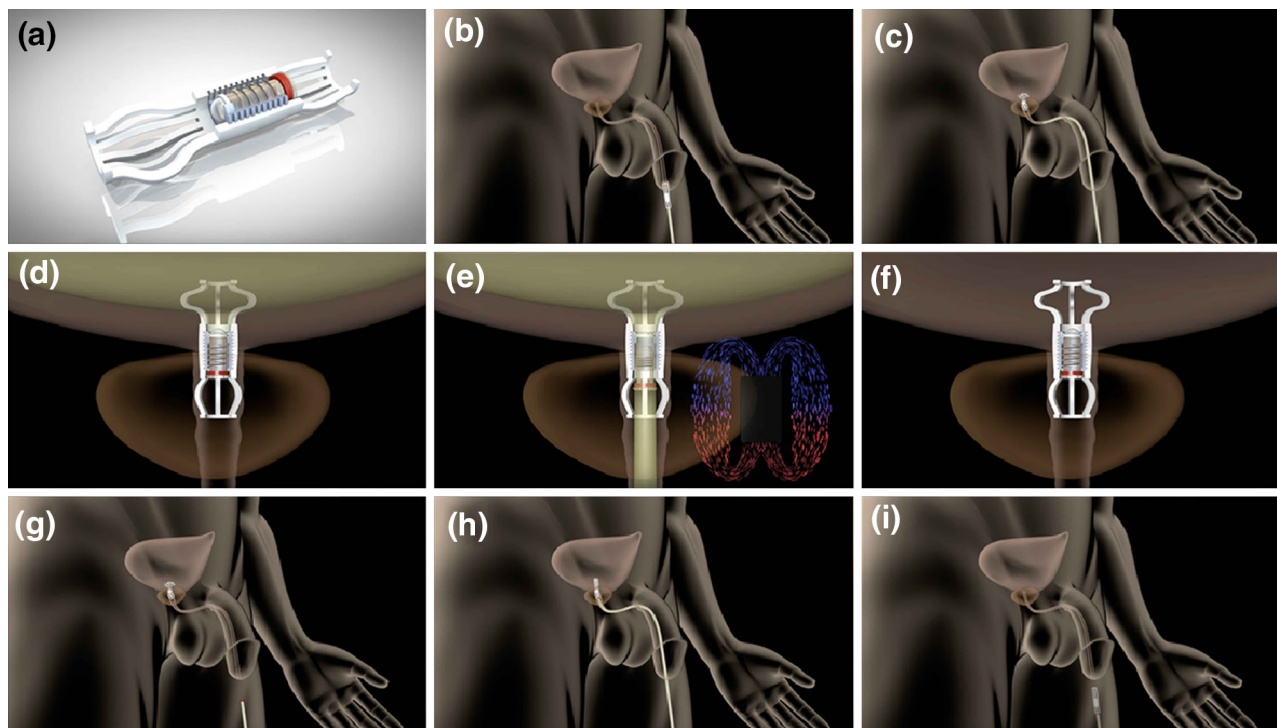


FIGURE 1. Concept depiction and device application steps. (a) depiction of the artificial sphincter and its internal components; (b) artificial sphincter insertion into the urethra *via* a catheter; (c) artificial sphincter positioning in correspondence to the bladder neck; (d) the device ensures the continence by exploiting a one-way polymeric valve, supported by a dedicated stiffening element connected to a spring; (e) once a suitable magnetic field is externally applied, the spring and the stiffening element shift down, thus decreasing the opening pressure of the polymeric valve and allowing bladder voiding; (f) once the magnetic field is removed, the artificial sphincter components restore the original configuration, thus guaranteeing continence; (g–i) the device is removed from the urethra in a minimally invasive way, using a catheter similar to the one used for inserting the device.

the distance between the internal magnet and the external one should be minimized. Moreover, orientation plays a key role: the two magnets can establish an efficient magnetic link if their magnetization axes are properly aligned. These considerations led to identify the perianal area as the most suitable one for positioning the external magnet, thus allowing urination. The distance between this area and the bladder neck is normally 8–9 cm for males and 4–5 cm for females (that is much less in comparison with other areas, e.g., the periumbilical one). In addition, positioning in such area implies that internal and external magnets are almost coaxial, thus maximizing magnetic attraction force in comparison with other positioning strategies.

Concerning IVPs, the medical constraints regarded: (1) a pressure value not to be exceeded during urination, thus to avoid non-physiological pressure profiles during miction and (2) a “safety” pressure value in correspondence to which the device must still guarantee continence. Concerning point (1), it is known that in healthy subjects, during urination, the IVP reaches a maximum peak of 6 kPa. When the IVP exceeds such threshold, it means that a subject suffers from bladder outlet obstructions.^{3,32} Thus, the targeted AS, once the safety system is deactivated, should not induce an IVP higher than 6 kPa during urination. Concerning point (2), it must be taken into account that IVP is the sum of the intraabdominal pressure from outside the bladder and the detrusor pressure exerted by the bladder wall musculature. When the safety system is active, the AS must guarantee continence even in correspondence to supra-physiological IVP values due to sudden abdominal contractions, efforts, *etc.* The scientific literature reports ~12 kPa as an IVP peak reachable during coughs, sport activities, or other daily life actions.³⁶ Thus, to guarantee continence with a certain safety margin (i.e., +33%), the device was designed to prevent urine flow for IVP values up to 16 kPa.

Description of the Operating Principle

The device was composed of seven parts (Fig. 2a): (i) an external case; (ii) a polymeric valve; (iii) a safety cursor; (iv) a spring chamber; (v) a spring; (vi) an internal magnet and (vii) a top plug. The external case embedded all parts: it had an outer diameter of 7.25 mm and a total length of 30 mm. The polymeric valve allowed a unidirectional flow of urine and was featured by a relatively small opening pressure (~6 kPa). The safety cursor was a hollow cylinder provided with a central circular element that went in contact with the valve, thus stiffening it and raising its opening pressure value up to 16 kPa, thus guarantee-

ing a hermetic closure of the system (and consequently continence) even in correspondence to high IVPs due to sudden abdominal muscle contractions. The spring stiffness was 0.02 N/mm, while its length was 8 mm. The spring chamber was designed to guarantee enough space for spring placement and to allow an easy assembly of the different components. The inner magnet had a hollow cylinder shape with an outer diameter of 6.35 mm, an inner diameter of 4.45 mm and a length of 9 mm. The top plug was designed to complete the device assembly thus constraining a suitable designed frame in nitinol which prevented the device slipping in the urethra (see next sections).

The block diagram shown in Fig. 2b describes the device operating principle. The two key elements determining the AS behavior are the polymeric valve and the safety system. The safety system consists of the safety cursor, the inner magnet, and the spring. When no external triggers are applied, the safety system is always on, due to the spring pre-load, which puts the safety cursor in contact with the valve. Thus, the system is in the left loop described in the figure and no urination occurs. When the external trigger is applied (through an external magnet), a magnetic coupling is established and the internal magnet is attracted in the opposite direction respect to the valve. This causes a small shift of the internal magnet, which compresses the spring and produces the translation of the safety cursor, which is no more in contact with the valve. Thus, the valve recovers its original small opening pressure. In this case, the system is in the right loop described in the figure and urination occurs.

AS Component Fabrication

The external case, the safety cursor, the spring chamber and the top plug were made of a diamagnetic material (ERGAL, aluminum alloy), easily machinable with a computer numerical control (CNC) machine with five axis (HSPC 2522, Kern, Olympiastraße, Germany). Each component was fabricated with a 0.05 mm accuracy. The polymeric valves were fabricated by exploiting dedicated molds, composed of two parts. Both cutting frame and molds were fabricated by using a 3D printer (HD3000 ProJet, 3D Systems, Rock Hill, USA). The custom blade was obtained by modifying the cutting edge of an off-the-shelf surgical blade (CHIMO size 22, Moretti s.p.a., Cavriglia, Italy). The material selected for valve fabrication was polydimethylsiloxane (PDMS, Sylgard 184, Dow Corning, Midland, USA). The valve fabrication process was based on the following steps: (1) PDMS preparation: monomer and curing agent were mixed with a 20:1 monomer/curing agent ratio, then the mixture was degassed for 20 min in a vacuum

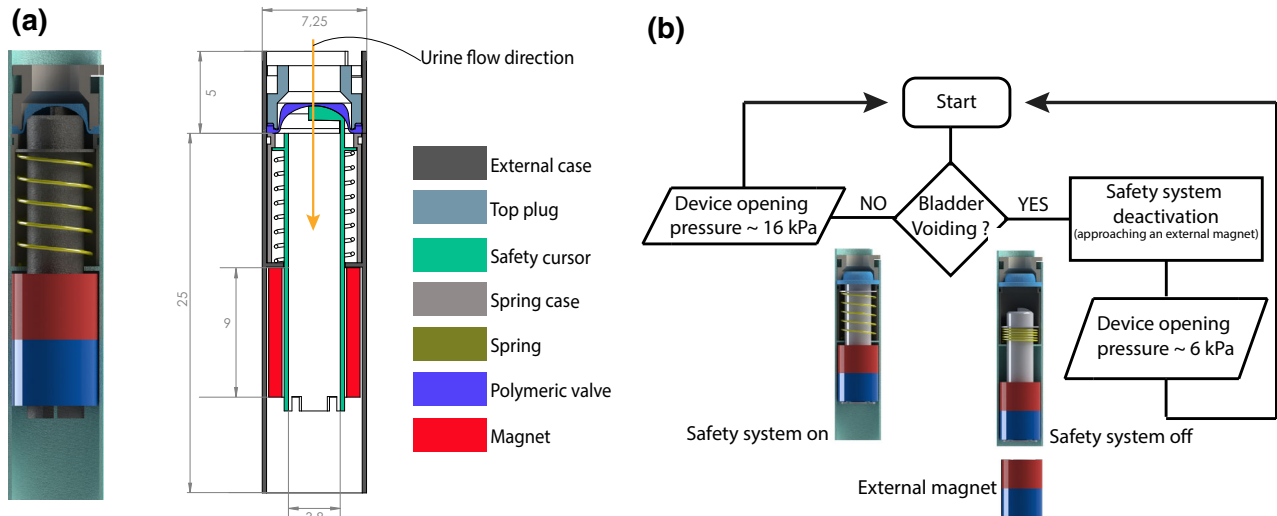


FIGURE 2. Artificial sphincter components and operating principle. (a) The main system components are shown, namely an external case, a top plug, a safety cursor, a spring chamber, a spring, a polymeric valve and an internal magnet. (b) Block diagram depicting the artificial sphincter operating principle: the safety system is normally active, thus the device guarantees continence through a high valve opening pressure (16 kPa). When the patient wishes to urinate, the safety system can be deactivated by approaching an external magnet to the body surface, with a proper orientation. Once the safety system is deactivated, the patient can urinate by simply contracting the bladder muscles which produce an intravesical pressure larger than 6 kPa, able to open the polymeric valve.

chamber. (2) Mold surface treatment: a thin Teflon film (LOCTITE 8192, Düsseldorf, Germany) was deposited by spraying it on the mold surface. (3) PDMS casting: once the mixture was well degassed, it was casted into the Teflon-coated mold. (4) Polymerization: after PDMS casting, the mold was closed and thermally treated at 90 °C for 3 h. (5) Valve extraction and cutting: the mold was opened and the polymeric valve removed. It was then subjected to die cutting by the dedicated frame and custom blade. The magnets were fabricated by Bassi-Group-International srl (Castelnovo di Sotto, Italy). All magnets were featured by an axial magnetization and a N52 grade. The spring was fabricated by RAM s.r.l. (Lucca, Italy) exploiting a 0.2 mm diameter wire made of AISI 316 steel (a non-magnetic material, extremely resistant to corrosion). The Nitinol structure was fabricated by using a single wire superelastic Nitinol alloy (0.4 mm diameter, SE508, NDC, Fremont, USA).

FEM Simulations

Matlab® R2013a (MathWorks, Natick, USA) and Abaqus 6.13 (Dassault Systemes, Waltham, USA) were used to manage data and to carry out FEM simulations, respectively, in order to evaluate the opening pressure of the polymeric valve and the opening pressure when the valve was constrained by the safety cursor. Simulations were carried out by using the hyperplastic Abaqus module. An explicit

dynamic behavior was defined, by imposing a mass scaling equal to 100. A structured Hex mesh made of 3492 cells was used for the polymeric valve. To identify the most suitable mesh for the target application, we carried out mesh refinement tests (Table S1). Material mechanical properties were properly taken into account in the simulations, by importing the real stress-strain curves experimentally obtained for the different material types (Fig. S2).

Set-Up for Bench Tests

The set-up used to test the polymeric valve and the overall AS performances *in vitro* consisted of a robot (Melfa RV-35B, Mitsubishi, Tokyo, Japan) provided with position control, managed by a program running in real-time and exploiting the external-mode feature of Simulink (MathWorks) environment. The Simulink program also managed pressure sensor data (HCX001D6V SensorTechnics, FirstSensor, Berlin-Oberschöneweide, Germany), acquired by an Arduino Due board (Arduino, Ivrea, Italy). Position control and data storage were managed at a frequency of 1 kHz. Pressure sensor data were filtered by using a 100 Hz bandwidth.

Ex Vivo Tests

Cadaver tests were performed on a female corpse available at a dedicated teaching and research surgical

center (iClo s.r.l., Arezzo, Italy), fully accredited for cadaver management. All procedures were carried out in a fully equipped surgical room, with proper individual protection devices and clothing. The corpse had the following features: age: 74; cause of death: lung cancer; height: 1.52 m; weight: 45 kg; gender: female; race: Afro-American. The cadaver showed a fully intact urinary system.

RESULTS

Design and Fabrication of the Unidirectional Polymeric Valve

The polymeric valve was designed to obtain a one-way system featured by a vault-like shape and a six-point star shape die-cutting on its top surface. The valve had an axial symmetry and nine geometrical parameters fully described its profile (Figs. 3a and 3b). FEM simulations allowed to predict the polymeric valve behavior when the valve top surface was loaded with a linear rising hydrostatic pressure, for different geometrical parameters and different material stiffness values (Fig. S3). Simulations allowed to identify the design parameters needed to obtain a polymeric valve with an opening pressure of ~ 6 kPa, namely $P1 = 3$ mm, $P2 = 50^\circ$, $P3 = 0.125$ mm, $P4 = 83^\circ$, $P5 = 0.5$ mm, $P6 = 0.25$ mm, $P7 = 83^\circ$, $P8 = 0.7$ mm and $P9 = 3.6$ mm. The material selected for valve fabrication was PDMS featured by a 20:1 monomer/curing agent ratio, corresponding to an elastic modulus of ~ 1.2 MPa²² (Fig. 3c, Video S2).

Once obtained a suitable valve profile with defined performance in terms of opening pressure, the valves were fabricated exploiting a mold and a dedicated frame with a custom blade for producing six-point star shape die-cutting on the top valve surface (Figs. 3d and 3e).

To validate the valve behavior, a proper set-up was designed (Fig. 3f). It was composed of: (i) a robot provided with a position control, (ii) a 60 mL syringe kept in vertical position by a frame, and (iii) a pressure sensor. The syringe outlet was connected to the polymeric valve through a flexible tube provided with a three-way T-joint. This also allowed a connection between the pressure sensor and the syringe outlet. The robot was exploited to manage the upstream pressure on the AS by changing the vertical position, and thus the liquid pressure. Figure 3g shows a representative pressure profile recorded during the polymeric valve testing, while Fig. 3h demonstrates that the valve opening pressure values derived from FEM predictions match well with the experimentally measured ones (6.13 ± 0.77 kPa).

Spring Dimensioning and Magnetic Interaction

FEM simulations were integrated with an additional element in order to simulate the safety cursor and the spring behavior, thus obtaining the device performance when the safety system was active. To this aim, a new element was added, namely a cylinder with a diameter of 0.8 mm composed of two parts: the first one, positioned in contact with the polymeric valve, was featured by the actual stiffness of the safety cursor material (safety cursor emulator); the second one was featured by a tunable stiffness in order to simulate springs with different stiffness values (spring emulator) (Fig. 4a).

The aim of these simulations was to identify a suitable spring stiffness in order to obtain a trade-off between (i) the device safety in correspondence to supra-physiological IVP values due to sudden abdominal contractions and (ii) the external magnet size. Simulation results highlighted that the AS opening pressure could be tuned by modulating spring stiffness: by increasing the spring stiffness, the opening pressure rose up to a maximum value of ~ 20 kPa, up to 0.04 N/mm (Fig. 4b). Based on above-mentioned medical specifications, a spring stiffness value of 0.02 N/mm could be considered suitable for our application, as it implied hermetic closure of the system for IVP values up to 16 kPa. Such elastic constant value (0.02 N/mm) represented a good trade-off between system safety at high pressures and relatively low dimensions of the external magnet needed to overcome the spring reaction force, when deactivation is needed.

The minimum required displacement of the safety cursor, allowing it not interfering with the valve deformation, was ~ 5.4 mm (Fig. S4). The desired displacement was set at 6 mm, thus slightly rounding up the minimum value. The spring length when fully compressed was 2 mm. Thus, overall, the initial spring length was 8 mm. The inner magnet size was consequently set, aiming at exploiting the free space still available in the device: it was a hollow cylinder with an outer diameter of 6.35 mm, an inner diameter of 4.45 mm and a length of 9 mm.

In order to validate the FEM simulations that took into account the safety cursor and the spring, a set-up similar to the one shown in Fig. 3f was used. Increasing pressure values were applied to the device, keeping each value constant for 4 s, to highlight possible valve pressure losses over time. Results demonstrated that the AS well sustained increasing pressure values, without pressure losses, when the safety system was switched on (Fig. 4c). Furthermore, its performances were in good agreement with the predictions derived from FEM simulations (opening pressure: 15.07 ± 1.2 kPa) (Fig. 4d).

Magnetic Artificial Urinary Sphincter

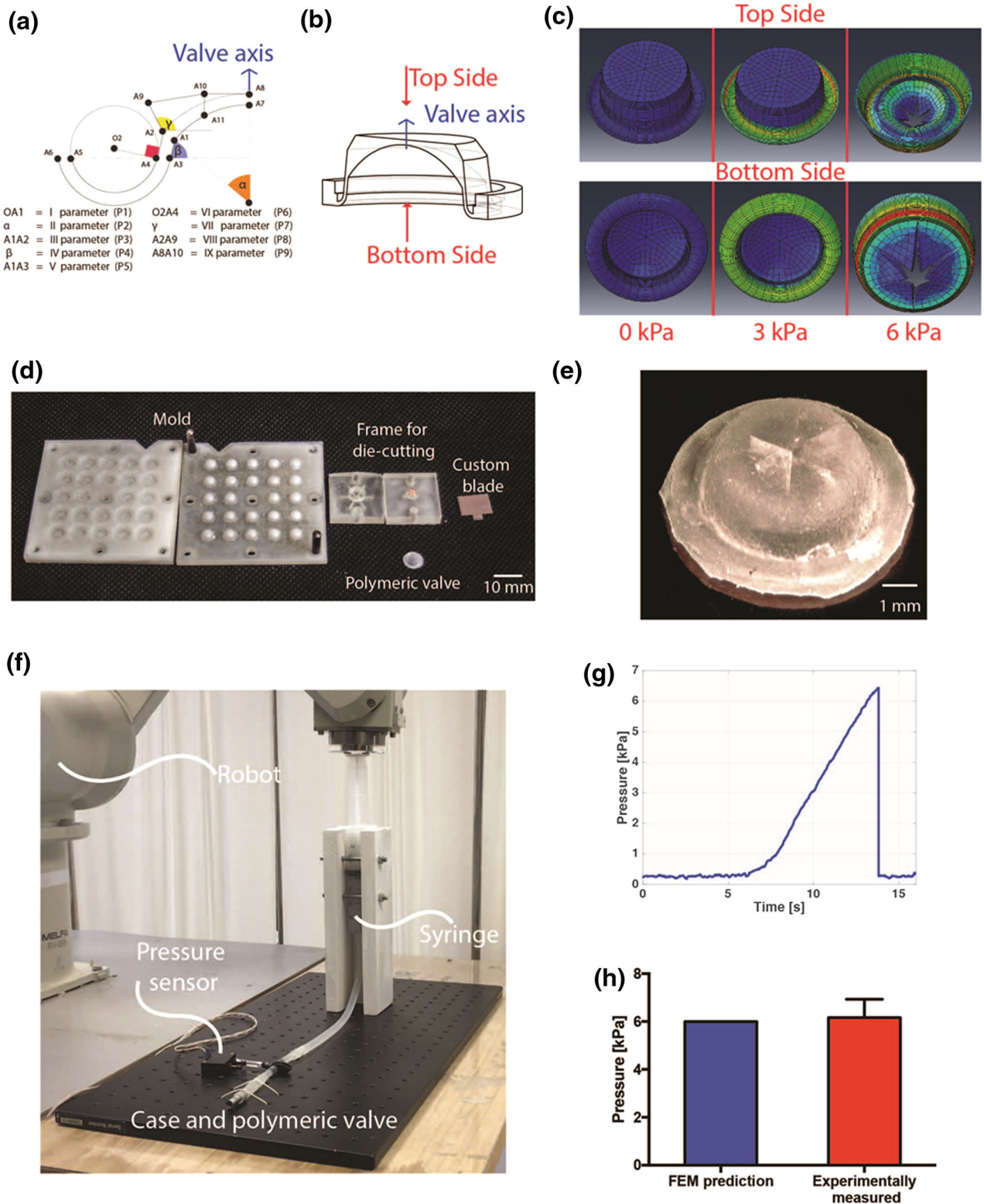


FIGURE 3. One-way polymeric valve design, fabrication, and testing. The valve was featured by nine geometric parameters (a) and an axial symmetry (b); it guaranteed hermetic closure up to a pressure threshold, beyond which it reached a cracking state that was simulated through FEM predictions (c). Once defined the valve profile and the material stiffness, the proposed valve was fabricated by exploiting a 3D printed mold, a custom frame for die-cutting and a small blade (d). (e) shows a fabricated polymeric valve. In order to test the valve behavior and thus validate FEM analyses, a custom experimental step-up was used (f). (g) shows a typical pressure profile for a valve, obtained during the mentioned tests, while (h) shows a comparison between the predicted valve performance, derived from FEM simulations, and the experimental measures. Four independent samples were analyzed and six measurements were performed for each sample.

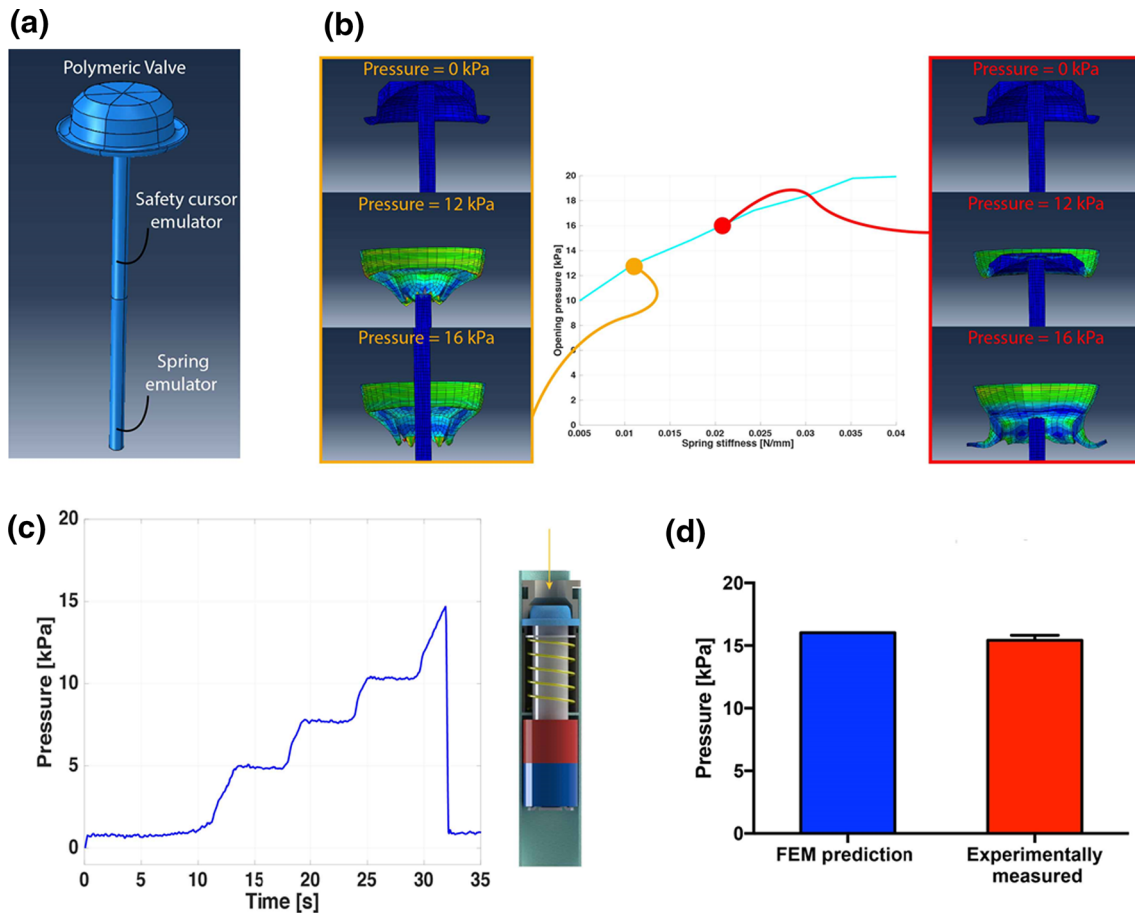


FIGURE 4. Safety system simulation and testing. Simulation results show that the safety system enhances artificial sphincter performances in terms of valve opening pressure, up to 20 kPa (a, b). An example of pressure profile overtime for the AS when the safety system is switched on is shown in (c), while a comparison between artificial sphincter performance FEM predictions and the experimental results is shown in (d).

The interaction between internal and external magnet guaranteed a proper magnetic coupling: the aim was to overcome the reaction force generated by the spring and to compress it, thus causing a 6 mm shifting of the safety cursor. Being the spring constant 0.02 N/mm, the force needed was 0.12 N, along the main AS axis. To calculate the external magnet features allowing the desired magnetic coupling, a discrete simulator was implemented and validated (Figs. S5 and S6), based on a well-established model.¹² The distance between the two magnets was fixed at 50 mm (assuming a female anatomy) and the resulting external cylindrical magnet dimensions were: 35 mm diameter, 20 mm height (axial magnetization).

Nitinol Structure for Device Positioning

A smart structure was needed for stably positioning the device at the bladder neck, thus avoiding its slippage along the urethra. Such structure should guarantee a large deformability in order to be inserted into

the cannula and, once pushed into the bladder, should be deployed, restoring the original shape. To this aim, a Nitinol wire with a diameter of 0.4 mm was selected. Nitinol is a shape memory alloy that, if properly preformed, is able to be deformed and then to easily recover its original shape.²⁵ The Nitinol wire was properly shaped at 823 K by exploiting a custom brass frame (Fig. 5a), to achieve a four wings-based structure with a maximum opening diameter of 45 mm (Fig. 5b). The superelastic behavior of the fabricated structure is shown in Fig. 5c and in Video S3.

Assembly and Testing of the Artificial Sphincter

After fabricating all device components (Fig. 6a), the AS was assembled in an integrated prototype, shown in Fig. 6b. Such prototype underwent bench tests as shown in Fig. 6c: the set-up was similar to the one shown in Fig. 3f, with the addition of two Plexiglas structures positioned at proper distances from the AS, thus reproducing the bladder neck level and the

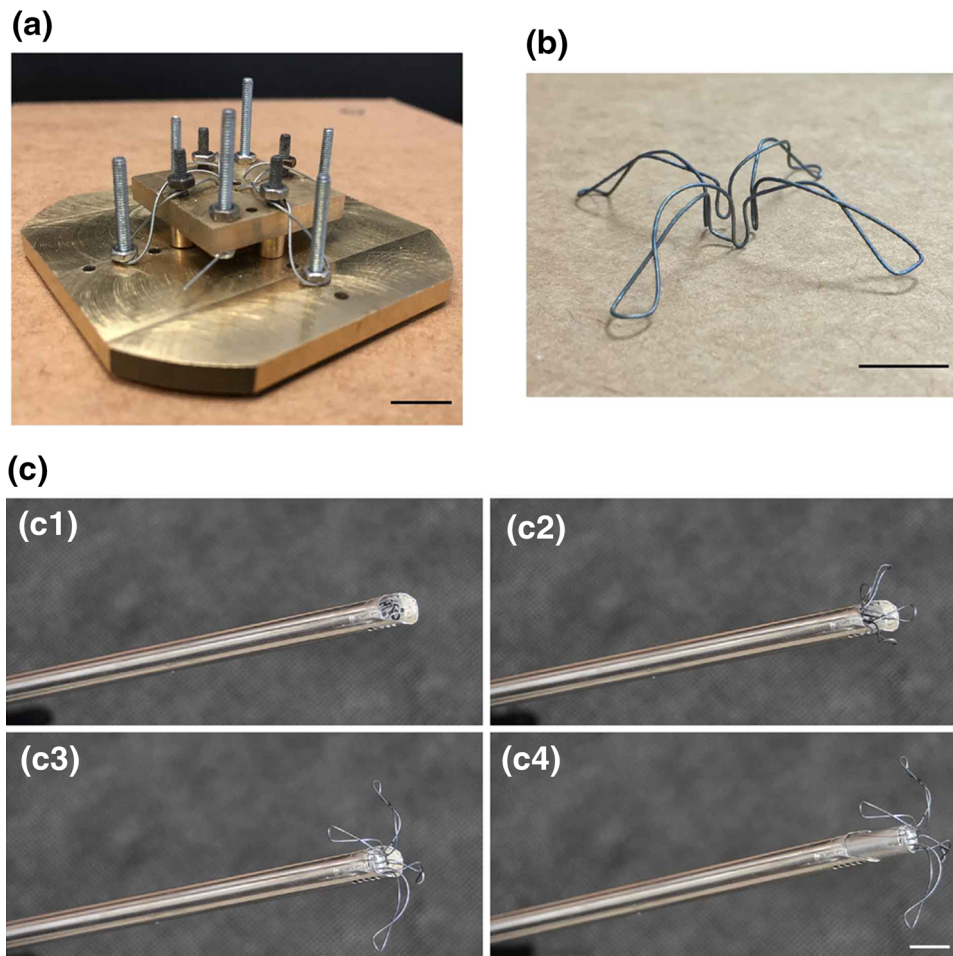


FIGURE 5. Nitinol structure for device positioning. (a) Frame used to forge the Nitinol wire in a predetermined shape. (b) Final wire shape. (c) Superelastic behavior of the Nitinol structure, mounted on the artificial sphincter external case: the four wings can be easily deformed in order to insert the device into a standard cannula for urethral insertion (C1); when the device is pushed out from the cannula, the Nitinol structure recovers its original shape (C3–C4). Scale bars = 10 mm.

body surface level. The AS was tested by applying an increasing pressure and keeping the different pressure levels constant for 4 s for highlighting possible pressure losses. The safety system resulted effective until a permanent magnet was positioned under the Plexiglas structure simulating the body surface level. The safety system was thus de-activated and a pressure drop was consequently immediately observed (Fig. 6d, Video S4). This result demonstrated the ability to properly control the switching of the system between the “on” and the “off” working conditions, by simply positioning a proper permanent magnet at a distance compatible with anatomical constraints.

A further experiment was carried out by exploiting the same set-up: first, the safety system was de-activated by placing the permanent magnet below the AS; second, the robot vertical speed was imposed to 16.31 mm/s, in order to achieve a flow rate of 10 ml/s, which is comparable with the one reached by healthy subjects during bladder emptying³; finally, the pressure

on the AS was raised until its opening pressure, thus causing polymeric valve opening and liquid flow through the system. The peak pressure recorded during liquid flow through the AS was ~ 6 kPa, which decreased immediately to a plateau of ~ 4.5 kPa (Fig. S7). Such pressure value implies that the AS introduced a mild resistance to urination, which is clinically acceptable.³² The total time needed to void a full bladder (standard volume: ~ 500 mL) would be ~ 50 s, which can be considered fully acceptable. Overall, bench tests highlighted the potential of the endourethral AS described for tackling UI disfunctions.

Ex Vivo Test on Human Anatomy

As final validation, an *ex vivo* test on female human anatomy was carried out. The test was performed on a supine female human cadaver provided with a complete and undamaged urinary system. First, the blad-

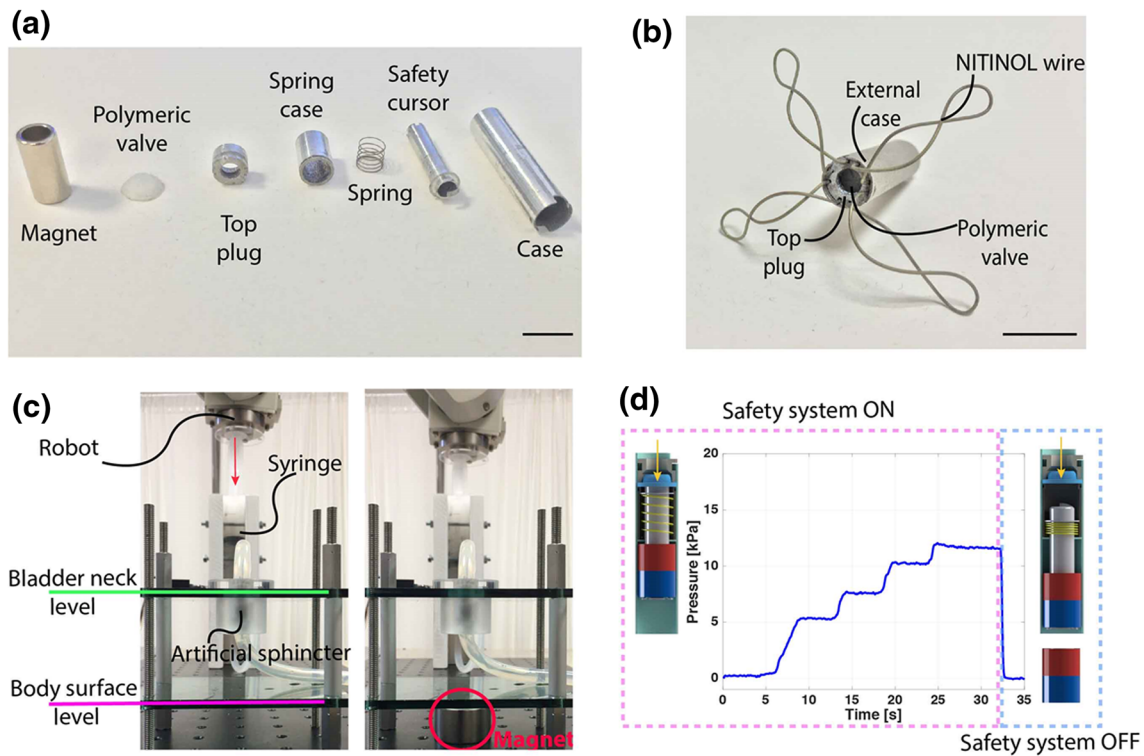


FIGURE 6. Artificial sphincter assembly and testing. (a) Device components: a permanent magnet, a polymeric valve, a top plug, a spring case, a spring, a safety cursor, and an external case. (b) Final assembled prototype. (c) Set-up used for the bench tests aimed at validating the artificial sphincter working principle. (d) Performance of the device tested. Scale bars = 10 mm.

der was exposed through appropriate incisions of the abdominal tissue layers. Then, the AS insertion was carried out by: (i) introducing a guide catheter into the urethra in order to guarantee an initial tissue dilation; (ii) introducing a well-lubricated cannula coaxially over the urethral guide catheter; (iii) introducing the AS into the cannula; (iv) pushing the AS toward the bladder by using a proper pusher, until the Nitinol structure recovered its shape and allowed device stabilization at the bladder neck; (v) removing the cannula.

The bladder was progressively filled of water by means of a syringe; the AS, with its safety system activated, guaranteed full continence in correspondence to large liquid volumes (~500 mL) introduced into the bladder and in correspondence to additional pressures that were manually and repeatedly applied on the organ. When the safety system was deactivated by approaching the external magnet to the body surface, the valve opened and urine started to flow, thus emptying the bladder. These phases are shown in Video S5.

Overall, the cadaver test demonstrated the ease of the device insertion procedure, the actual disappearing nature of the system, which does not alter the body scheme and the overall device usability and efficacy in guaranteeing continence and, when desired, in allow-

ing urination by simply approaching an external permanent magnet to the body surface (properly orienting it along the urethra and thus the AS main axis).

DISCUSSION

The aim of this work was the design, fabrication and validation of a novel AS to face UI, overcoming the drawbacks of already existing solutions. Overall, the results demonstrate that the proposed device is intrinsically featured by two different opening pressure levels, depending on its activation/deactivation status. In its deactivated status, the system allows urine to flow freely in the urethra, if the IVP overcomes 6 kPa (Figs. 3g and 3h). This is due to the specific design and stiffness of the polymeric valve (Figs. 3a–e, S3), which is the core of the device. On the other hand, in its activated configuration, the device guarantees hermetic closure even at high IVP values (up to 16 kPa, Figs. 4c and 4d).

The ability to switch between an “off” condition (device open) and an “on” condition (device closed) is the hallmark of the most advanced endourethral and extraurethral systems existing at present. However, state-of-the-art devices use rather complex/invasive means to switch between the two mentioned modalities,

i.e., manual pumps,²⁸ remotely controlled hydraulic/pneumatic systems,^{13,18,30} inflatable balloons,¹⁰ *etc.* The AS described in this paper has the key advantage of relying on a simple magnetic coupling between an internal and an external magnet, which acts as a trigger for switching between the two system configurations (Fig. 6d).

From an engineering viewpoint, the magnetic activation strategy described in the paper can be considered more effective in comparison with other possible de-activation/activation means, e.g., exploiting a coil-based device instead of a permanent magnet. In fact, such a coil would imply a significant power consumption to generate a suitable attraction force. This may cause device overheating, with consequent danger for the patient during handling in case of device failure. In addition, a complex device that needs on-board battery and control electronics could cause the object to fall into a higher biomedical device class, thus increasing the difficulties of a certification pathway for the system.

In order to guarantee the correct de-activation of the safety system, an accurate alignment between the external and the internal magnets is required. Thus, it could be argued that the de-activation procedure is not really immediate to perform by the patient, and this may be identified as a weak point of the system. However, if any orientation of an external magnet would be able to open the device, being in proximity of a magnetic field would bring inevitably to the safety system deactivation. Instead, by establishing a preferential magnet orientation, the device opens only when requested by the patient, with really few chances of an undesired opening. We expect that a short training and simple signs on the magnet to identify north and south poles would be enough to let the patient understand the correct orientation to be applied to the magnet. Thus, such apparently negative aspect is actually an important feature of the device, which guarantees a high degree of safety.

From a clinical viewpoint, such strategy may have a clear impact concerning urination management of incontinent patients. This may imply a drastic reduction of the psychological burdens that are typically associated to this dysfunction.

The AS described in this study shows clear advantages in terms of therapy efficacy in comparison with conservative solutions normally employed to manage UI.^{1,19,29,31,34} In addition, the device shows significantly lower invasiveness if compared with other non-conservative therapeutic devices, especially extra-urethral ones, which usually require surgical procedures to be installed and subsequent hospital admission.^{6,7,9,10,13,18,27,28,30,37} This is a clinically relevant aspect, which may allow to significantly ameliorate

patients' recovery from interventions and to reduce the costs for the whole healthcare system.

Compared with other endourethral devices, the AS described in this study also shows clear advantages. In fact, it avoids practical limitations, psychological burdens and infection risks typical of catheters. The Femsoft system¹⁰ is a disposable single use oil-filled sleeve that conforms to the anatomy of the urethra and bladder neck, to reduce leakage of urine. It needs to be removed and discarded each time that the subject wants to urinate. Afterwards, a new device must be inserted. This implies a considerable cost, due to the use of several devices per day. The AS described in this study is designed to chronically remain in the urethra for several months, without the need of frequently replacing it. Moreover, the Femsoft system is a unisex device (it can be applied only to women), while the prototype described in this paper is a unisex device. Finally, the Femsoft system slightly alters the body scheme (a small wire remains outside of the body and is visible), while the AS described in this paper is a fully disappearing system, with no externally visible parts. The device described in this paper has a magnetic field-based activation principle, as in the InFlow. However, such commercial product is not designed to fully guarantee continence, but it is rather a pump normally used to completely empty the bladder.⁵ Thus, it cannot be considered a competitor in the field of artificial sphincters to restore patients' continence. In addition, also the InFlow system is not a unisex device (it is usable only by women) that slightly alters the body scheme.

Thus, the AS described in this paper can be considered a proof of concept that considerably outperforms all the existing extraurethral and endourethral devices aiming at facing UI. Despite of its intriguing features, the device shows some limitations, in its current version. They should be properly addressed in a future evolution of the system, which will be needed to address product certification, animal tests and clinical trials.

The first issue concerns material biocompatibility. The materials used to fabricate the device to be considered relevant in terms of biocompatibility are the following: aluminum alloy (external case—conceived to be in contact with the urethra epithelium), PDMS (valve—expected to interact with urine) and Nitinol (anchoring device—conceived to be in contact with the bladder epithelium). The internal magnet and its nickel coating are mounted within the safety cursor structure (Fig. 2a) and thus they are not in contact with any tissue or body fluid. PDMS is widely used as synthetic substrate for cell culture and for *in vivo* implants, thanks to its high biocompatibility.²¹ Nitinol is also considered a material featured by a very good bio-

compatibility and widely used in the biomedical field to develop sutures, stents, *etc.*^{16,33} Aluminium alloys are less biocompatible, as they may release metallic ions, which could produce harmful effects on cells in the medium/long-term. In a future evolution of the prototype, more suitable materials will be selected for fabricating the device, in order to minimize harmful interactions with the surrounding tissues. For example, all the rigid parts of the device could be made of highly biocompatible titanium alloys, or coated with biocompatible polymers/hydrogels.

The second issue concerns material encrustation. The formation of encrustations on urological devices is an unsolved issue, at present. In fact, after a certain period, all devices must be replaced, as no polymeric material is able to resist urine for more than few weeks.¹¹ The Nitinol structure and the PDMS valve are expected to be chronically in contact with urine. This is not expected to negatively affect the function of the Nitinol structure (which has simply to remain in its position), but it may significantly affect the performance of the PDMS valve, in terms of opening pressure and overall reliability. To face this issue, *ad hoc* surface functionalization strategies may be carried out,¹⁷ in order to provide polymeric valves with a urine-resistant additional thin layer. In any case the problem of long-term reliability of the device is mitigated by its easy and straightforward replacement strategy. Preclinical and clinical trials will define an acceptable time slot for the implantation, compatible with a simple removal/replacement process. The envisaged limited cost of the device makes reasonable to plan relatively frequent (even monthly) replacements.

The third issue concerns a proper anchoring of the system. In fact, the current device guarantees high stability only in one direction, thanks to the nitinol stent that prevents the artificial sphincter to slip down along the urethra and to be expelled from the body (Fig. 5, Video S3). However, a second distal stent would be also needed to avoid possible device slippage into the bladder. This may be achieved by using another shape memory alloy structure or an inflatable balloon positioned at the distal portion of the device. Friction enhancement between the device external case and the urethral lumen may represent an alternative strategy to guarantee the device long-term stability, to be evaluated through *ad hoc* preclinical analyses.

CONCLUSION

This study demonstrates the feasibility of a novel magnetically controlled endourethral artificial sphincter to address urinary incontinence. The paper focuses on the device design, fabrication and validation both

in vitro (bench tests) and *ex vivo* (on a human cadaver). Results highlight that the opening pressure of the endourethral valve embedded in the device can be easily modulated by simply approaching/removing a permanent magnet to/from the perineal area, thus allowing the patient to easily manage his/her urination, when desired. When no magnetic inputs are provided, the device guarantees continence even at high bladder pressures, up to 16 kPa, a value that exceeds the pressures generated as a consequence of coughs, sport activities and sudden abdominal contractions. The proof of concept reported in this study should be ameliorated in terms of material biocompatibility, material-urine interaction and reliability of the anchoring system. However, this device has the potential to considerably outperform all the existing extraurethral and endourethral devices for the management of urinary incontinence and shows promises for a future clinical translation. This technology may imply a drastic reduction of the psychological burdens that are typically associated with urinary incontinence.

ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (doi: [10.1007/s10439-016-1784-2](https://doi.org/10.1007/s10439-016-1784-2)) contains supplementary material, which is available to authorized users.

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