Characterisation of human urethral injury thresholds to develop mechanisms for preventing urinary catheter inflation related injuries

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Abstract

Background

There are no studies that characterise the relevant thresholds of human urethral tissue mechanics pertaining to urethral injury during inadvertent inflation of a catheter balloon in the urethra. Such information is pertinent to developing mechanisms to prevent catheter related injuries.

Objective

To characterise urethral diametric stretch and urinary catheter inflation pressure thresholds that precede human urethral injury.

Materials and Methods

Human male urethras were obtained from patients undergoing male to female gender reassignment surgery. The anchoring balloon of 12Fr urinary catheters were inflated in the bulbar urethra using a syringe pump apparatus. Urethral diametric stretch and catheter balloon pressure were recorded. Urethral injury was characterised macroscopically using visual inspection and microscopically using immunohistochemistry, Masson's trichrome and Verhoeff-Van Gieson stains.

Results

No damage (n=3), tearing (n=3) and rupture (n=3) of samples was observed following catheter balloon inflation. Human urethral tissue injury (tearing or rupture) occurred at an external urethral diametric stretch ≥1.26 and balloon inflation pressure ≥120kPa. Significant relationships were identified between urethral wall thickness and the level of trauma induced during catheter balloon inflation (p=0.001). Furthermore, there was

significantly higher collagen content identified in samples that experienced no damage compared to those that underwent injury (p=0.038). Ruptured urethras demonstrated complete transection of collagen, elastin and muscle fibres.

Conclusions

This study demonstrates that injury occurs in male urethras at an external urethral diametric stretch ≥1.26 or with balloon inflation pressures >120kPa. These findings are important as contemporary catheters routinely generate inflation pressures that are significantly higher.

Statement of Significance

Despite the preventable iatrogenic morbidities and associated medicolegal costs secondary to urethral catheterisation related injuries, few studies examine mechanisms to prevent such incidences. Of those studies that examine mechanisms, none are based on data obtained from testing of human urethras. This study characterises the relevant mechanics of human urethral tissue in order to further develop mechanisms to prevent urinary catheter related injuries. This study demonstrates that human male urethra injury occurs at an external urethral diametric stretch ≥1.26 or with balloon inflation pressures ≥120kPa. Iatrogenic injuries will therefore continue to occur as contemporary catheters routinely generate significantly higher inflation pressures. Safety mechanics must therefore be introduced using findings derived from appropriate models such as those outlined in this study.

Key words: Urethral trauma, Urethral injury, Urinary catheter, Urethral rupture

1.0   Introduction

Approximately 25% of hospitalised patients undergo urethral catheterisation (UC) during their inpatient stay [1]. Of these, 0.3%-0.7% will sustain iatrogenic urethral trauma secondary to inadvertent inflation of the catheter's anchoring balloon in the urethra [2,3]. Short-term complications associated with traumatic UC are penile/perineal pain, urosepsis, acute urinary retention, urethral bleeding or urinary tract infection [1]. Long-term complications include urethral stricture disease with subsequent reconstructive procedures [3,4]. Despite these preventable iatrogenic morbidities, few studies examine mechanisms to prevent UC related injuries [5]. Of those that examine such mechanisms, none are based on data obtained from testing of human urethras [6]. This study seeks to characterise the relevant mechanics of human urethral tissue in order to further develop mechanisms to prevent urinary catheter related injuries. To achieve this the urethral diametric stretch and catheter balloon inflation pressure thresholds that precede human urethral injury are characterised during intentional inflation of a urinary catheter anchoring balloon in the bulbar urethra of explanted human male urethras.

2.0 Methods

2.1 Patient Characteristics

Following hospital ethical research committee approval, human urethras were obtained from 9 consenting patients undergoing male to female gender reassignment surgery at the University Hospital Essen, Essen, Germany. The mean age was 40 ± 13.13 years (range: 18-58 years). Samples were maintained at *in vivo* length by tethering the urethra to a urinary catheter during surgical excision. All samples included the bulbar urethra at the proximal end, the penile urethra and the glans of the penis at the distal end. The glans was excised prior to testing to facilitate mounting of the samples in a custom fabricated catheter inflation apparatus.

2.2 Preparation of human urethras

Human urethras were stored at -20°C within 2 hours of excision. This method of storage was employed as it has been previously demonstrated to have no significant effects on biological soft tissue mechanical properties once the tissue is unfrozen [7,8]. Prior to testing, samples were defrosted overnight at 4°C and subsequently immersed in distilled water at 37°C to equilibrate the tissue back to physiological temperature on the day of testing. Prior to testing, *in vivo* length and external diameter of samples was measured using Vernier callipers. Measurements were confirmed using a non-contact photography method. The mean *in vivo* length of the samples was 147.44±13.97 mm (range: 122.96-167.76 mm). Samples were then marked with acrylic paint at points 5 cm from each end. This distance was then measured to allow for restoration of samples to *in vivo* length and to ensure proper alignment of the samples in the catheter inflation apparatus.

2.3   Catheter-Inflation Testing

Samples were mounted in the apparatus demonstrated in figure 1. Physiological humidity and temperature were achieved during testing by submersing the samples in a distilled water bath maintained at 37°C. Each end of the sample was mounted on stainless steel tubular mounts (OD = 6.5 mm, ID = 5 mm) lined with 60 grit sandpaper and secured with wire hose clips of internal diameter ranging from 9-13 mm. Samples were then aligned and restored to *in vivo* length. A 12Fr Coloplast© silicone urinary catheter was inserted into the sample via the proximal hollow tubular mount and the tip was secured in a recess in the distal mount. This method ensured that the anchoring balloon of the catheter was in the bulbar urethra prior to inflation. The anchoring balloon was then inflated with 10 ml of saline via a syringe (BD, USA) and a syringe pump (Pump Systems Inc., USA, Model: NE-1000) at an inflation rate of 30 ml/min [6]. No more than 10 ml of saline was injected into each catheter anchoring balloon as to do so would not be clinically representative. The resulting pressure was monitored using a calibrated 1 bar pressure transducer (Sensortecknic, USA). The corresponding change in sample outer diameter was monitored using a video extensometer (Messphysik, Austria). Although it is possible to record pressure-diametric stretch relationships from this testing (Supplementary Figure 1), such data should not be

2.4   Histology and Immunohistochemistry

Masson's trichrome and Verhoeff-Van Gieson stains were employed to histologically evaluate trauma to epithelium, collagen and elastin within the urethral extracellular matrix (ECM) following testing. Small ring segments (approx. 5mm) were cut from the traumatised region and adjacent non-traumatised region of samples and fixed traction-

free in 10% formalin, embedded in paraffin, and then sliced into 10 μm thick segments. Immunohistochemical staining of muscle actin was also used to identify the smooth and striated muscle content of the samples. Images of the stained samples were obtained using a Nikon microscope (Eclipse, 90i) at 4x and 20x for gross and detailed imaging respectively. The composition of each sample was assessed from the histological images using a previously outlined protocol which employs ImageJ to convert collagen composition to the mean Gray value of the blue colour intensity of the Mason's Trichrome stains with respect to tissue area (Bauman et al., 2014). This protocol uses hue (121-179), saturation (20-255) and brightness (10-255) to isolate collagen from stained images and is also adapted for elastin and muscle content. Both elastin and muscle content are identified using the YUV colour space (elastin: Y=0-120, muscle: Y=0-145, both: U and V=0-255). Morphological characterisation of the sample lumen was performed by examining the adjacent non-traumatised histological sections using ImageJ and recording lumen area, perimeter and major/minor axis length. Major and minor axis lengths consider the profile of the sample lumen to be an ellipse and refer to the maximum and minimum diameter of this ellipse respectively.

2.5   Statistical Analysis

Statistical analysis was performed using Minitab 17 (Minitab Inc. State College, PA, USA). Correlations between the variables were assessed using 2-tailed parametric bivariate analysis and regression analysis was performed to examine the relationship between theses variables. Statistically significant differences were identified between groups of continuous variables using 2-tailed t-tests. A p value <.05 was considered statistically significant.

3.0   Results

3.1   Catheter-Inflation Testing

Two distinct forms of urethral injury were observed following catheter balloon inflation: rupture (n=3) and tearing (n=3) as illustrated in figure 2. Rupture is defined as complete separation of urethral tissue and tearing is defined as partial separation of urethral tissue. The type of urethral trauma sustained by each sample, the inflation pressure/diametric stretch at which it occurred, the sample thickness, the length of the lumen major axis and collagen content are demonstrated in table 1. Urethral external diametric stretch is calculated as the urethra outer diameter at the location of the catheter balloon and at the point of complete balloon inflation, divided by the original urethra outer diameter, at the same location, prior to balloon inflation.

Figure 3 demonstrates the significant relationships identified between the balloon inflation variables and the sample characteristics through parametric bivariate analysis. Figure 3A displays representative images of samples that underwent no damage (n=3), tearing (n=3) and rupture (n=3) following catheter balloon inflation. Figure 3B demonstrates the negative relationship between maximum external diametric stretch and the maximum inflation pressure required to inflate the catheter anchoring balloon (p=0.007). This figure also reveals that the threshold values for maximum external urethral diametric stretch and catheter balloon inflation pressure that precede urethral injury (tearing or rupture) for this cohort of samples are 1.26 and 120kPa respectively. Figure 3C demonstrates that a significant relationship was not identified between anchoring balloon inflation pressure and the level of urethral trauma. Figure 3D demonstrates the negative relationship between the level of urethral trauma and the thickness of the urethral wall (p=0.001). Figure 3E demonstrates the

significantly higher collagen content identified in samples that experienced no damage compared to those that sustained injury (p=0.038). No further significant relationships were identified between the level of urethral trauma and any of the remaining sample parameters. Figure 3F demonstrates the negative relationship between the inflation pressure required to inflate the catheter anchoring balloon and the major axis length of the sample lumen (p=0.004). Figure 3G demonstrates the positive relationship between maximum diametric stretch and the major axis length of the sample lumen (p=0.045). All additional sample parameters characterised in this study are listed in supplementary table 1.

3.2   Histological Examination

Histological examination was performed to examine the effect of anchoring balloon inflation on the microstructure of the urethral ECM. Sections of the urethra in which the anchoring balloon was inflated are shown in figure 4. Figure 4A demonstrates the gross effects of catheter anchoring balloon inflation on urethral ECM. Figure 4B evaluates the microscopic structure of urethral tissue samples that sustained no damage following anchoring balloon inflation (n=3). In this group, elastin fibres are dispersed throughout the ECM and are most dense in the middle and inner layers. Long striated muscle fibres are present in the outer layer of the urethra with smooth muscle in the middle layer. Collagen occurs as wavy coiled bundles of fibres in the outer layer of the urethra. Figure 4C evaluates the microscopic structure of urethral tissue samples that experienced tearing following anchoring balloon inflation (n=3). Elastin, muscle and collagen fibres appear frayed and separated. Figure 4D evaluates the microscopic structure of urethral tissue samples that ruptured following anchoring balloon inflation (n=3). Complete disruption and transection of collagen, elastin and

muscle fibre is observed in this group. Disruption of the epithelial layer is also evident in the MTC stain (indicated with an arrow).

4.0   Discussion

This current study investigates the relationship between external urethral diametric stretch, catheter anchoring balloon inflation pressures and urethral trauma during UC in *ex vivo* human urethral models. Results show that urethral injury can occur at external urethral diametric stretch ≥1.26 and catheter balloon inflation pressures ≥120kPa. These findings are important as contemporary catheters and catheter syringes have been unchanged for decades and can routinely generate inflation pressures >700kPa [6,9,10].

This study also characterises and grades urethral trauma macroscopically using visual inspection and microscopically using immunohistochemistry. Two types of urethral injuries are identified, specifically 'tearing' and 'rupture', due to anchoring balloon inflation within the bulbar urethra. Previously, internal diametric stretch and maximum catheter balloon inflation pressure thresholds have been investigated as indicative parameters for urethral trauma during UC in porcine models. In porcine urethras, internal urethral diametric stretch >1.6 and/or a maximum anchoring balloon inflation pressure >150kPa results in urethral rupture [6]. In the present study, the minimum pressure value for human urethral rupture is similar at 120kPa (for the thinnest sample) and the mean balloon inflation pressure in the samples that underwent rupture is 165.16±56.68kPa (Table 1). These threshold pressure values highlight the dangers inherent with a misplaced anchoring balloon as they are significantly lower than the aforementioned standard UC inflation pressures.

This mechanical urethral data also provides important novel information on urethral distension and pressure profilometry. Considerable variations in urethral lumen major

axis length measurements are identified indicating the highly variable anatomy and luminal geometry of the male urethra. As expected, the pressure required to inflate the catheter balloon decreased as urethral lumen major axis length increases. Similarly, maximum external diametric stretch also increases with increasing lumen major axis length. These findings are intuitive as the catheter balloon can undergo increased expansion in a wider urethral lumen before contacting and traumatising urethral tissue. Variations in vessel wall thickness and collagen content account for the spectrum of urethral trauma identified. Thinner urethras were more likely to rupture and thicker urethras were more likely to experience no damage when exposed to the anchoring balloon inflation pressures. This is also intuitive as thicker samples will experience a lower induced stress due to the force of the inflating balloon being applied to an increased cross sectional area, which will increase with increasing wall thickness. Similarly, samples with a higher collagen content were less likely to experience injury relative to samples with a lower collagen content.

These histological findings also conform to the severity of urethral injury that results from traumatic UC. In ruptured urethras, collagen, elastin and muscle fibres were completely transected thus indicating the long-term potential for urethral stricture disease. Urethral stricture occurs due to scarring of the spongy tissue of the corpus spongiosum and most urethral strictures are the result of trauma. When urethral epithelium is breached, the scarring process extends through the tissues of the corpus spongiosum into adjacent tissues leading to contraction of the scar and reduced urethral lumen. These mechanical and histological findings demonstrate that traumatic UC transects urethral epithelium which is a major risk factor for scar and subsequent stricture formation.

These findings are clinically relevant as millions of urinary catheters are inserted annually and iatrogenic urethral injuries are a potentially preventable source of injury in patients [14]. Iatrogenic complications from UC are associated with medicolegal implications, financial penalties, longer inpatient stays and long-term urethral stricture disease. In addition to short-term and long-term iatrogenic morbidity and monetary loss, urethral injuries lead to an increased burden on urological resources, inpatient beds and skill use. Recently, the incidence, cost, complications and clinical outcomes of iatrogenic urethral catheterisation injuries was prospectively monitored across 2 tertiary referral teaching hospitals and the incidence of urethral trauma was 6.7 patients per 1,000 patients catheterised. Furthermore, 81% of patients with urethral trauma sustained a Clavien-Dindo complication ≥grade 2 and the cost of managing these inpatient complications was €335,377 over a 6-month period [1]. To decrease or eliminate the risk of urethral injury during UC, urologists must be willing to advocate for safer urethral catheter design modifications using mechanical and histological findings derived from appropriate models such as those outlined in this study. Adjustments and improvements to catheter mechanics will likely result in an incremental decrease in iatrogenic urethral trauma.

A potential limitation of this study is that urethral samples in the present study were embedded solely in the corpus spongiosum without the supportive corpus cavernosum, fascial dartos and skin layers. These supporting structures reinforce the urethra and the inflation pressures leading to urethral injury identified in this study may underestimate *in vivo* inflation injury pressures. However, intentional inflation of a catheter balloon in an *in vivo* urethra is unethical. Therefore, the novel transgender model described herein provides a reasonable estimation of inflation pressure

thresholds with an additional safety factor incorporated as the supporting structures that reinforce the urethra *in situ* are absent. Furthermore, this study only considers the bulbar urethra. Future studies should seek to inflate catheter anchoring balloons in the membranous and prostatic urethra, two other common locations for misplaced catheter inflation. However, these urethral regions are retained by the patient during transgender surgery and therefore a separate model to the one described in this study is required. Although samples were obtained from patients engaged in long term oestrogen hormone treatment, there is no literature to suggest that hormone therapy alters the structure and mechanics of the urethra or surrounding tissues. Additionally, oestrogen has been identified in the penises of men not engaged in hormone therapy and is believed to play a role in blood vessel regulation [15]. Therefore, the effects of hormone treatment on sample mechanics and composition in this study were not considered. It is also important to acknowledge that the sample size examined in this study is limited and that there is considerable variance in patient age. However, patient age was not found to correlate significantly with any of the mechanical, compositional or geometrical sample parameters determined in this study.

5.0   Conclusion

In human male urethras, this study demonstrate that urethral injury occurs at an external urethral diametric stretch ≥1.26 or with balloon inflation pressures ≥120kPa. These findings are important as contemporary catheters routinely generate inflation pressures that are significantly greater. This means that iatrogenic urethral injuries will continue to occur unless safety mechanics are introduced to standard urinary catheters using mechanical and histological findings derived from appropriate models such as those outlined in this study.

Acknowledgements

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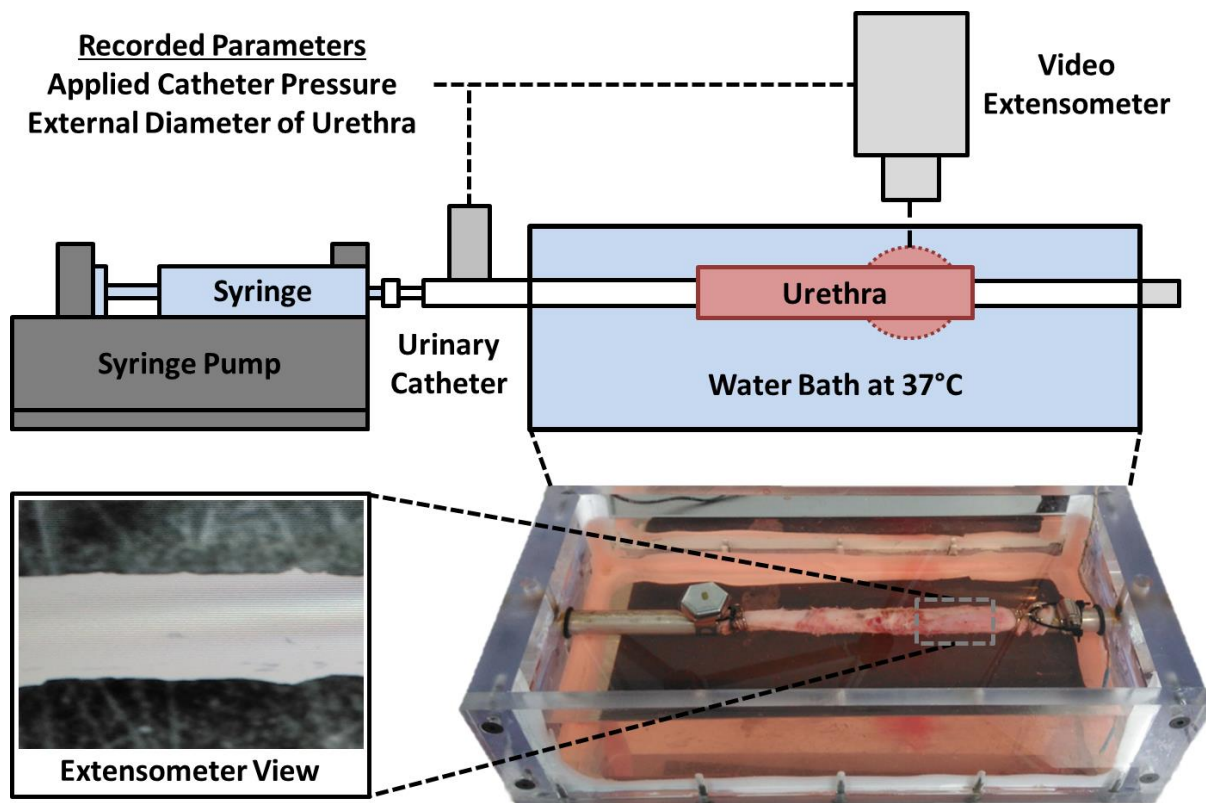
Figure 1: Schematic of the experimental apparatus used to perform inflation testing of urinary catheters in human urethral samples.

Legend: Male explanted urethras were mounted on stainless steel tubular mounts and secured. Samples were then aligned and restored to *in vivo* length. A 12Fr silicone urinary catheter was inserted and secured in a recess in the distal mount to ensure that the anchoring balloon of the catheter was in the bulbar urethra prior to balloon inflation. The anchoring balloon was then inflated with 10 ml of saline via a syringe and a syringe pump.
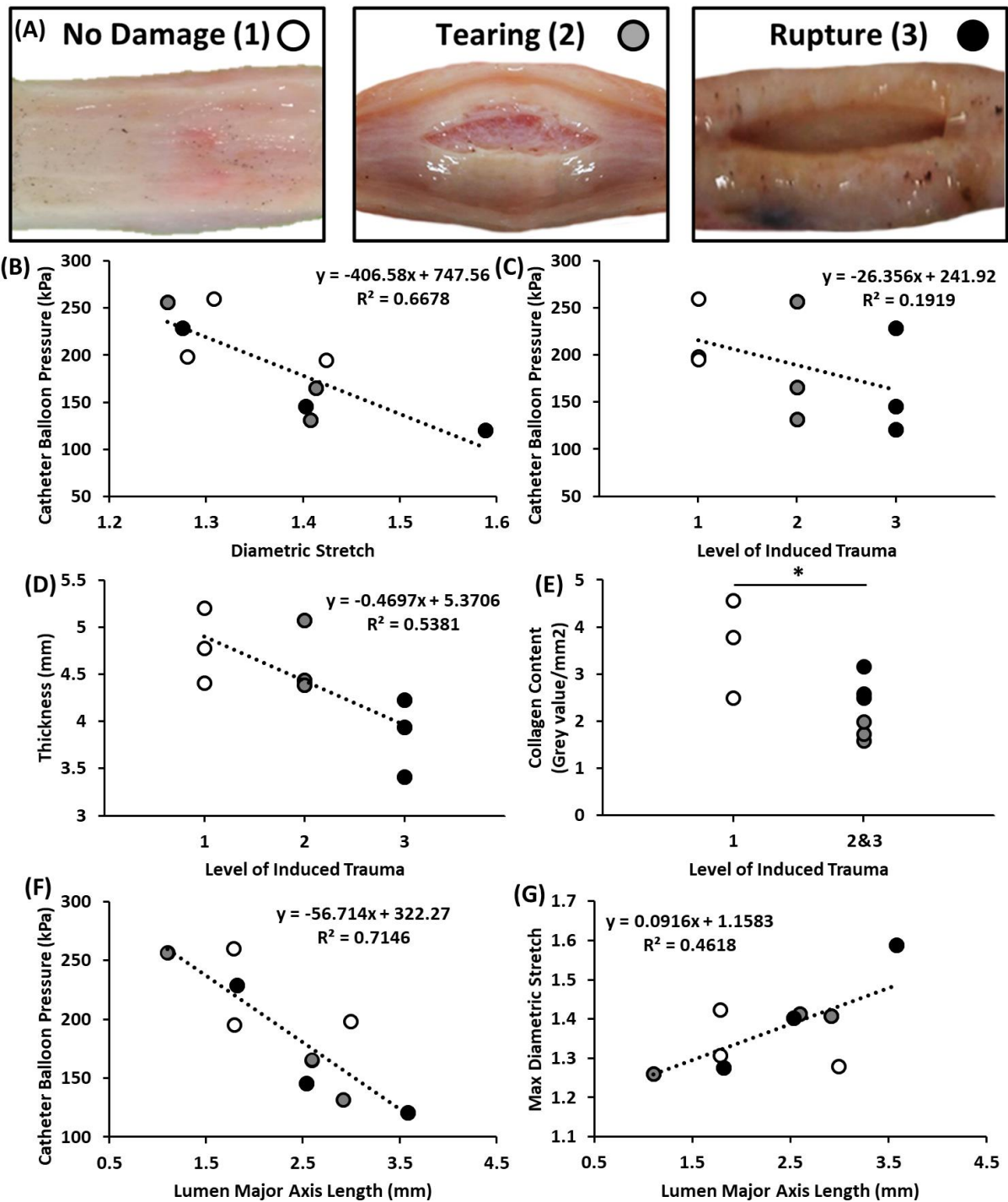
Figure 2: A) Representative images of urethra samples that experienced no damage (n=3), tearing (n=3) and rupture (n=3) following inflation of a urinary catheter anchoring balloon in the bulbar male urethra. B) Relationship between the maximum external diametric stretch of the sample and the inflation pressure required to inflate the catheter anchoring balloon. C) Relationship between urethral trauma and catheter

balloon pressure. 1 corresponds to no damage (open circles), 2 corresponds to tearing (grey circles) and 3 corresponds to rupture (black circles). C) Relationship between urethral trauma and thickness of the urethral wall. D) Significantly higher collagen content identified in samples that experienced no damage compared to those that underwent tearing or rupture. E) Relationship between the maximum external diametric stretch of the sample and the inflation pressure required to inflate the catheter anchoring balloon. F) Relationship between the pressure required to inflate the catheter anchoring balloon and the length of the major axis of the sample lumen. G) Relationship between the maximum external diametric stretch of the sample and the length of the major axis of the sample lumen.
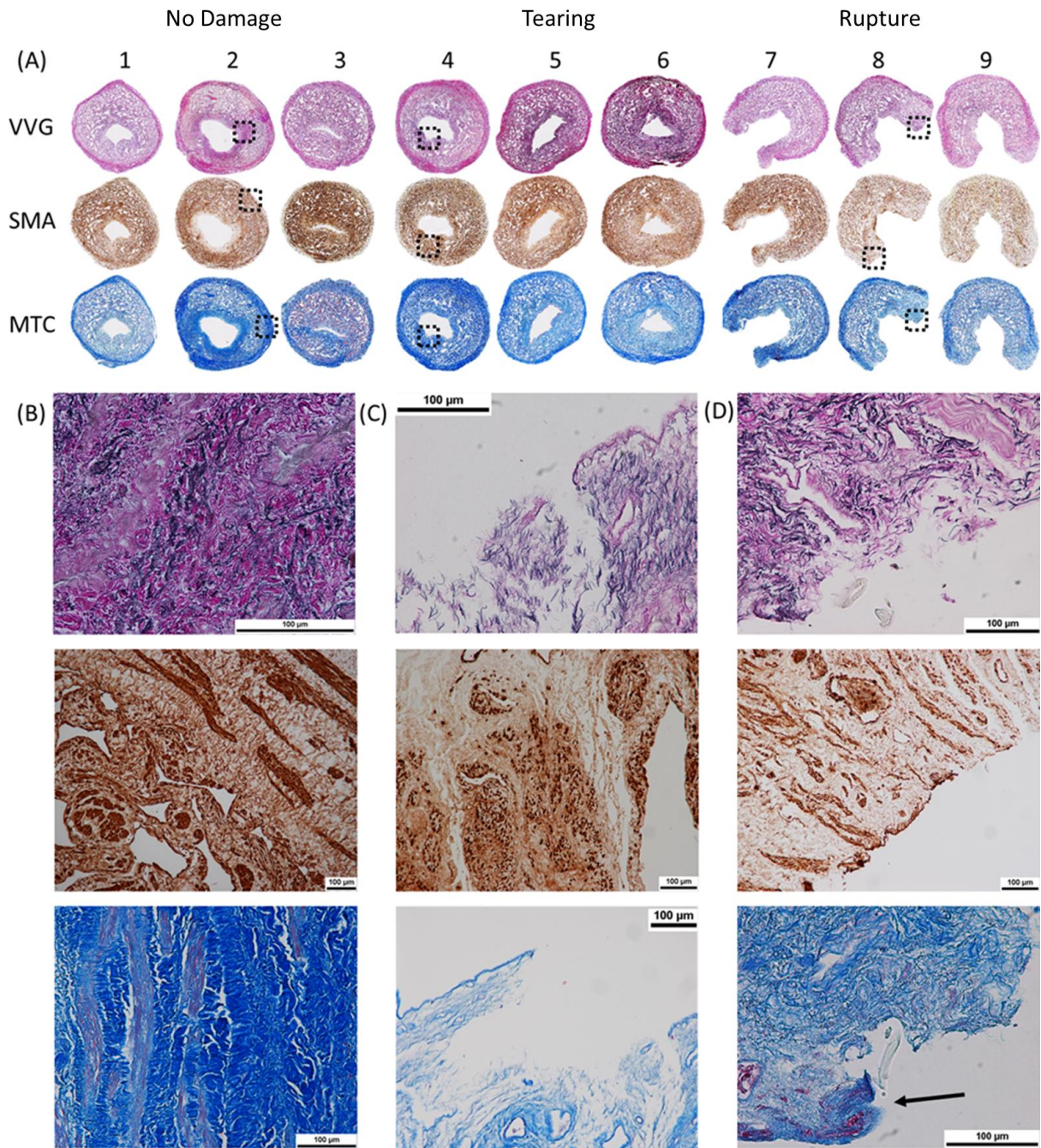
Figure 3: A) Histological stains depicting the effects of catheter balloon induced trauma on urethral ECM. B) Urethral ECM of samples that sustained no damage despite balloon inflation in the bulbar urethra. Fibres of elastin are dispersed throughout the ECM and are most dense in the middle and inner layers. Long striated muscle fibres are present in the outer layer of the urethra with smooth muscle occurring in the middle layer. Collagen occurs as wavy coiled bundles of fibres in the outer layer of the urethra. C) Splitting of urethral tissue is observed in urethral samples

that experienced tearing. Elastin, muscle and collagen fibres are frayed and separated. D) Complete transection of collagen, elastin and muscle fibres is observed in the samples that experieinced rupture. Disruption of the epithelial layer is also evident in the MTC stain (indicated with an arrow).

Sample	Trauma Type	Inflation Pressure (kPa)	External Diametric Stretch	Wall Thickness (mm)	Lumen Major Axis Length (mm)	Collagen Content (Gray value/mm2)
1	None	198.36	1.28	5.21	2.99	2.49
2	None	195.23	1.42	4.78	1.79	3.78
3	None	260.02	1.31	4.41	1.79	4.57
4	Tearing	165.54	1.41	5.07	2.59	1.73
5	Tearing	131.62	1.41	4.44	2.92	1.59
6	Tearing	256.61	1.26	4.39	1.1	1.99
7	Rupture	120.7	1.59	3.41	3.58	2.59
8	Rupture	228.98	1.28	4.23	1.82	2.5
9	Rupture	145.79	1.4	3.94	2.53	3.16

Table 1: Urethral trauma sustained, the inflation pressure/diametric stretch at which trauma occurred, the sample thickness, the length of the lumen major axis and the collagen content of each sample.

Legend: The threshold for human urethral injury occurred at an internal urethral diametric stretch ≥1.26 and balloon inflation pressure ≥120kPa. Urethral external diametric stretch was calculated by dividing the urethra outer diameter, at the location of the catheter balloon and at the point of complete balloon inflation, by the original urethra outer diameter, at the same location, prior to balloon inflation.

Sample	Age (years)	Trauma Type	Inflation Pressure (kPa)	External Diametric Stretch	Wall Thickness (mm)	Lumen Area (mm²)	Lumen Perimeter (mm)	Lumen Major Axis Length (mm)	Lumen Minor Axis Length (mm)	Collagen Content (Gray value/mm²)	Elastin Content (Gray value/mm²)	Muscle Content (Gray value/mm²)
1	45	None	198.36	1.28	5.21	3.58	12.58	2.99	1.52	2.49	6.57	9.97
2	18	None	195.23	1.42	4.78	1.11	14.52	1.79	0.79	3.78	2.34	13.85
3	36	None	260.02	1.31	4.41	0.82	9.81	1.79	0.59	4.57	2.38	11.08
4	50	Tearing	165.54	1.41	5.07	4.45	21.28	2.59	2.19	1.73	2.82	5.59
5	44	Tearing	131.62	1.41	4.44	0.54	13.30	2.92	0.24	1.59	6.36	1.77
6	58	Tearing	256.61	1.26	4.39	0.39	13.05	1.1	0.46	1.99	2.95	1.70
7	55	Rupture	120.7	1.59	3.41	4.03	12.25	3.58	1.43	2.59	3.47	13.64
8	25	Rupture	228.98	1.28	4.23	0.98	14.79	1.82	0.68	2.50	8.50	6.28
9	44	Rupture	145.79	1.4	3.94	1.25	19.04	2.53	0.63	3.16	2.30	21.49

Table S1: Details of all parameters examined in this study for each human male urethra sample.