



# Combined Dorsal Plus Ventral Double Tunica Vaginalis Graft Urethroplasty: An Experimental Study in Rabbits

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## OBJECTIVE

To investigate the efficacy of a combined dorsal plus ventral double tunica vaginalis graft for urethral reconstruction in a rabbit model through radiology and histopathology.

## METHODS

Thirty adult male New Zealand rabbits were randomly divided into 6 groups as follows ( $n = 5$ ): normal, stricture, and experimental groups A, B, C, and D. In the stricture and experimental groups, the ventral urethra was incised longitudinally, and the dorsal and ventral urethral mucosa were partially removed. Then,  $3 \times 20$  mm and  $5 \times 20$  mm tunica vaginalis grafts were obtained to repair the dorsal and ventral urethral mucosa defects, respectively, and the spongiosum was closed in the experimental groups. The urethral defects were not repaired in the stricture group. The rabbits in experimental groups A, B, C, and D were sacrificed at 2 weeks, 4 weeks, 12 weeks, and 24 weeks postoperatively, respectively, and the rabbits in the stricture group were sacrificed at 4 weeks postoperatively. The urethra was harvested for histological analysis. Urethrography was performed before sacrifice in the stricture group and experimental groups B and D.

## RESULTS

The retrograde urethrogram showed that all rabbits in experimental groups B and D had a patent urethra. Histological examination showed that the tunica vaginalis graft completely integrated into the urethra at 4 weeks postoperatively and transformed into a urinary pseudostratified epithelium at 12 weeks postoperatively.

## CONCLUSION

Combined dorsal plus ventral double tunica vaginalis graft urethroplasty is a feasible technique for urethral reconstruction in a rabbit model. UROLOGY 126: 209–216, 2019. © 2019 Elsevier Inc.

Male urethral stricture, a common urological disease, is one of the most challenging problems for urological surgeons. Many procedures are available to manage urethral stricture, including urethral dilatation, urethral stenting, internal urethrotomy, and urethroplasty,<sup>1</sup> and the performance of these procedures is heavily dependent on the stricture length, location, and degree of local fibrosis. For long anterior urethral strictures, substitution urethroplasty has become the standard procedure.<sup>2</sup> For a very tight long anterior urethral stricture containing oblitative or nearly oblitative sections, either tube augmentation urethroplasty

or staged urethroplasty are potential options. Tube augmentation urethroplasty is associated with a high failure rate and thus generally is not recommended.<sup>3</sup> Although staged urethroplasty provides good results,<sup>4</sup> the procedure is complicated. In 2008, Palminteri et al<sup>5</sup> first performed urethroplasty using a combined dorsal plus ventral double buccal mucosa graft and obtained encouraging results.

Many materials are available for substitution urethroplasty, including a preputial graft,<sup>6</sup> full-thickness skin graft,<sup>7</sup> oral mucosa,<sup>8</sup> bladder mucosa,<sup>9</sup> tunica vaginalis,<sup>10</sup> and colonic mucosa,<sup>11</sup> of which the oral mucosa is the most versatile clinically. However, harvesting the oral mucosa can cause donor site morbidity.<sup>12</sup> Moreover, limited sources of substitution material are available for a long and complicated urethral stricture.<sup>13</sup> The tunica vaginalis, which is an extension of the peritoneum, is a fibrovascular connective tissue covered by mesothelium. Its application as a substitution material for urethroplasty, both experimentally and clinically, has shown encouraging results.<sup>10,14,15</sup> The advantages of the tunica vaginalis include a shortage of hair follicles, ease of manipulation, good tensile, and physical properties enabling resistance to handling and availability in sufficient quantities.<sup>16</sup>

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In our study, we created an experimental model of a urethral defect and then repaired it using tunica vaginalis grafts applied on the dorsal and ventral surfaces of the urethra. We investigated the long-term efficacy of the technique through radiology and histopathology.

## MATERIALS AND METHODS

### Study Design

All experimental animal procedures were approved by the Institutional Animal Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology. A total of 30 adult male New Zealand rabbits weighing 2.5-3.0 kg were included in this study and were randomly divided into 6 groups as follows (n = 5): normal, stricture, and experimental groups A, B, C, and D.

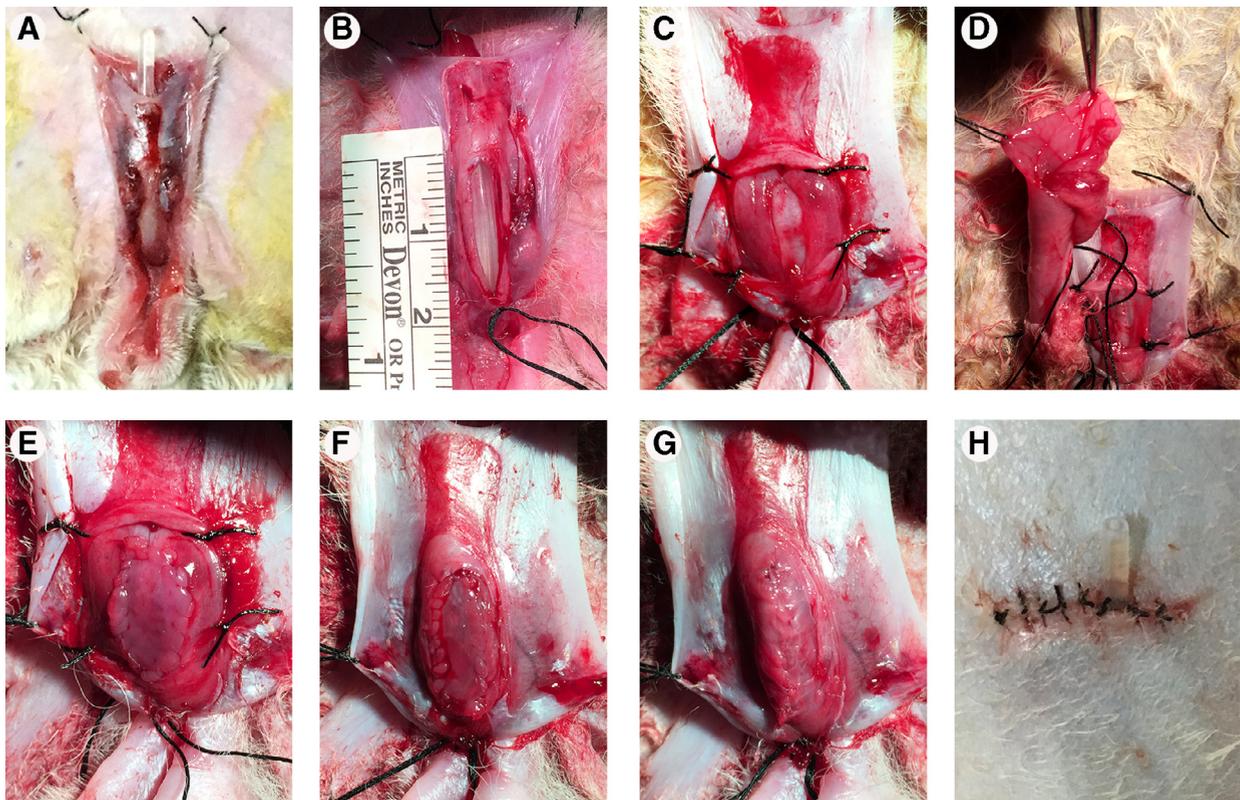
### Generation of Urethral Stricture Models

A urethral stricture was created in the rabbits in the stricture and experimental groups using our previously reported bleomycin injection technique.<sup>17</sup> Briefly, bleomycin (Nippon Kayaku, Tokyo, Japan) was dissolved in phosphate-buffered saline (0.01 M, pH 7.4) at a concentration of 1 mg/mL. The rabbits were restrained with the help of an assistant. A 50- $\mu$ L syringe with a 30-gauge needle containing bleomycin was

inserted into the urethral submucosal tissue every other day for 4 weeks to develop a mild urethral stricture model simulating the compromised urethral microenvironment.

### Anesthesia and Surgical Procedure

The rabbits in the experimental (A, B, C, and D) and stricture groups were anesthetized with intravenous pentobarbital (30 mg/kg) and fixed in the supine position. The area was disinfected with povidone-iodine solution after the scrotum and genital organ were shaved. The penis was dissected free from the anus, and an 8F catheter was inserted into the urethra (Fig 1A). The ventral urethra was incised longitudinally approximately 2 cm from the external urethral orifice, and a small part of the ventral urethral mucosa was removed (Fig 1B). The exposed dorsal urethra was incised in the midline. The margins of the incised dorsal urethra were dissected from the tunica and partially removed to create an oval area over the tunica albuginea (Fig 1C). The skin and dartos of the scrotum were incised, and the tunica was incised longitudinally to obtain the tunica vaginalis graft (Fig 1D). A 3  $\times$  20 mm tunica vaginalis graft was placed by dorsal inlay and quilted to the corpora to augment the dorsal urethral plate (Fig 1E). A 5  $\times$  20 mm tunica vaginalis graft was placed by ventral onlay and sutured to the urethral lateral margins to augment the ventral urethral plate (Fig 1F). The spongiosum was closed over the graft (Fig 1G). Then, the reconstructed urethra was covered



**Figure 1.** Urethral reconstruction with a combined dorsal plus ventral double tunica vaginalis graft. (A) The penis was dissected free from the anus. (B) The ventral urethra was incised longitudinally, and a small part of the ventral urethral mucosa was removed. (C) The dorsal urethra was incised in the midline and dissected to both sides to create an oval area. (D) The tunica vaginalis graft was harvested. (E) The dorsal urethral defect was repaired by tunica vaginalis graft in an inlay fashion. (F) The ventral urethral defect was repaired in an onlay fashion. (G) The spongiosum was closed over the graft. (H) Suprapubic cystostomy using an 8F catheter was performed. (Color version available online.)

with the bulbospongiosus muscle before the subdermal layer and skin were closed and marked by nonabsorbable sutures for future reference. A suprapubic cystostomy using an 8F catheter was performed to prevent urinary retention (Fig 1H). In the stricture group, the defects of the dorsal and ventral urethral mucosa were not repaired before the subdermal layer and skin were closed. All procedures were performed by the same surgeon with the assistance of an operating microscope. The rabbits in the normal group did not undergo any urethral operations.

### Postoperative Care

All rabbits were kept in rabbit cages and allowed free access to food and water. The suprapubic catheter was left in place for 4 weeks. The catheter was left indwelling for 7 days and irrigated with 0.1% povidone-iodine solution once daily. The rabbits received 40,000 U/kg/d penicillin intramuscularly for 7 days.

### Retrograde Urethrography

Retrograde urethrography was performed 4 weeks after surgery in the stricture group and experimental group B before sacrifice to evaluate the short-term therapeutic effect. Additionally, the procedure was performed 24 weeks after surgery in experimental group D to evaluate the long-term therapeutic effect. An 8F catheter was placed in the urethral orifice, and X-ray images were obtained after injection of iodine contrast into the urethra under general anesthesia.

### Histological and Immunohistochemical Analyses

The rabbits in experimental groups A, B, C, and D were sacrificed 2 weeks, 4 weeks, 12 weeks, and 24 weeks after the procedure, respectively. The rabbits in the stricture group were sacrificed 4 weeks after the procedure. After the rabbits were sacrificed, their urethras were harvested and fixed in 10% buffered neutral formalin. Cross sections of tissue specimens were stained with hematoxylin-eosin (H&E), Masson's trichrome (MT), and immunohistochemical (IHC) examination with an anti-alpha smooth muscle actin antibody (Abcam) for smooth muscle and an uroplakin II (UP-II) antibody (Biocare Medical, Concord, MA) for the urothelium following routine protocols.

### Statistical Analysis

Our goal was to compare differences in the diameters of the stricture and experimental groups by using retrograde urethrography. The urethral diameter results were measured 4 and 24 weeks after surgery. The urethral diameter results were also compared with those of the normal group. The results were expressed as the mean  $\pm$  standard deviation. The statistical analysis was performed with GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA) using a *t* test or 1-way analysis of variance. *P* < .05 was considered statistically significant.

## RESULTS

None of the rabbits died during the study period. No technical problems were encountered during the procedure. No complications, such as urethral fistula, urethral diverticulum, or urinary retention, occurred during the study period.

### Retrograde Urethrography

All rabbits in the stricture group showed a narrow urethral lumen 4 weeks after the procedure (Fig 2B). Comparatively, all

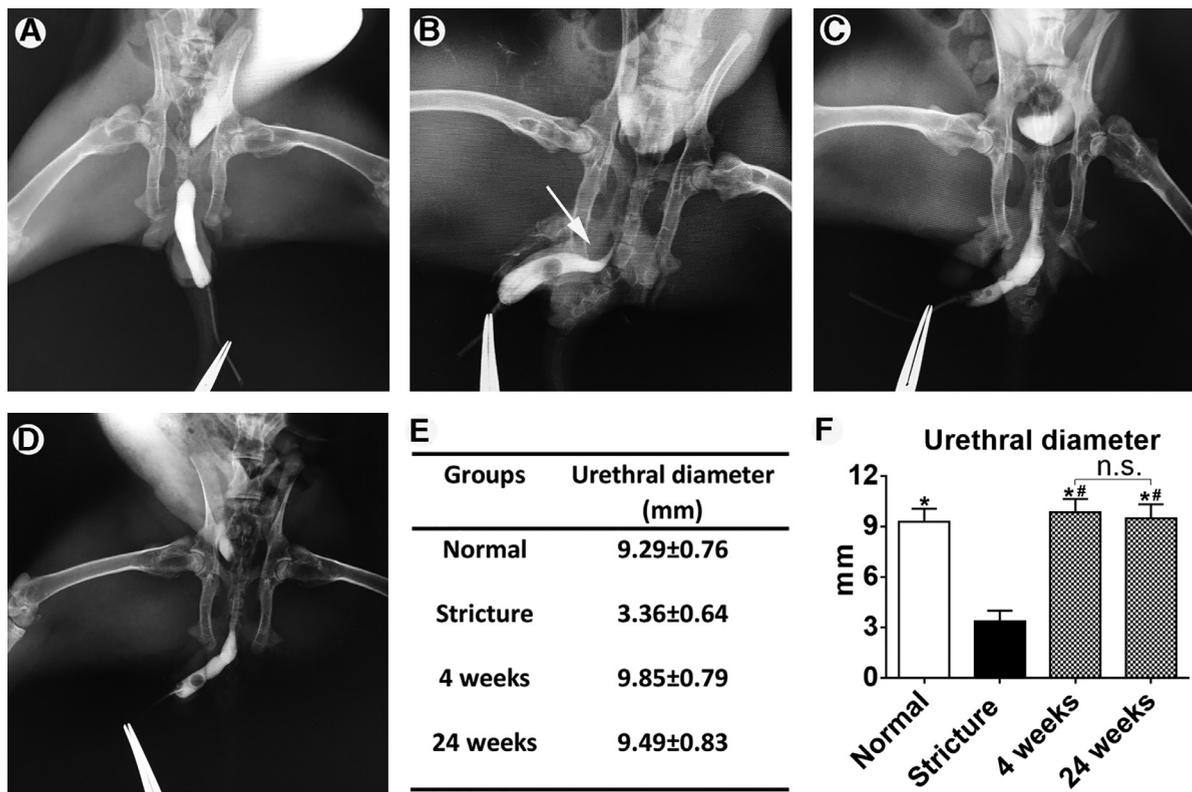
rabbits in experimental groups B (Fig 2C) and D (Fig 2D) showed a wide urethral caliber similar to that of the normal group (Fig 2A), indicating that the experimental rabbits could maintain a wide urethral caliber at 4 and 24 weeks postoperatively.

The mean urethral diameters of the normal, stricture, and experimental groups B (4 weeks) and D (24 weeks) were  $9.29 \pm 0.76$ ,  $3.36 \pm 0.64$ ,  $9.85 \pm 0.79$ , and  $9.49 \pm 0.83$  mm, respectively (Fig 2E). Compared with the stricture group, the experimental (4 and 24 weeks after surgery) and normal groups showed significant changes in the urethral diameter. However, no differences in the urethral diameter were found between the normal and experimental groups (4 weeks, *P* = .291; 24 weeks, *P* = .712), and between experimental groups B and D (*P* = .500) (Fig 2F).

### Histological and IHC Analyses

In experimental group A (2 weeks), the H&E-stained sections showed that the tunica vaginalis graft survived in the urethral lumen and that the transition area between the normal urethra and tunica vaginalis graft could be discerned. Slight inflammatory cell infiltration in the submucosa was observed. The MT-stained sections showed that the submucosal collagen bundles of the tunica vaginalis graft had a connection with those of the normal urethra (Fig 3A). In group B (4 weeks), the H&E-stained sections showed that the tunica vaginalis graft was completely integrated in the urethra. Inflammatory cells were rarely observed in the submucosa. The MT-stained sections showed that the submucosal collagen bundles of the tunica vaginalis graft could be discerned from those of the normal urethra (Fig 3B). In group C (12 weeks), the H&E-stained sections showed that the tunica vaginalis graft covered the pseudostratified epithelium. The MT-stained sections showed that the orientation of the collagen bundles and smooth muscle layers in the tunica vaginalis graft region resembled that in the normal urethra (Fig 3C). In group D (24 weeks), the epithelium was intact, and the structure of the tunica vaginalis graft could barely be discerned. The smooth muscle fibers were sparse in the position of the tunica vaginalis graft (Fig 3D).

In the stricture group, the H&E-stained sections showed a narrow urethral lumen with deficient epithelial layers and slight inflammatory cell infiltration in the submucosa (Fig 4A). The MT-stained sections showed severe fibrosis with some irregularly arranged collagen bundles and loose interspersed smooth muscle fibers (Fig 4B). The IHC analysis with the anti-alpha smooth muscle actin antibody for smooth muscle showed packed smooth muscle fibers and richly endowed vessels in the normal group. The stricture group showed loose interspersed smooth muscle fibers and sparse vessels. Experimental group C (12 weeks) showed regularly arranged smooth muscle layers and richly endowed vessels, which resembled those of the normal urethra (Fig 4C). The IHC examination with the UP-II antibody for the urothelium showed an intact urothelial layer in the normal group. The stricture group showed deficient epithelial layers on the dorsal and ventral urethra. Experimental group C (12 weeks) showed an intact urothelial layer (Fig 4D). The native urethra covered the stratified urothelial lining (Fig 4E). The mesothelial lining of the tunica vaginalis graft was replaced by a pseudostratified uroepithelial lining (Fig 4e). The covering epithelial lining of the tunica vaginalis grafts was homogeneous and relatively thinner than that of the native urethra.



**Figure 2.** Retrograde urethrogram. (A) Urethral caliber of the normal rabbits. (B) The stricture group showed a narrow urethral lumen. (C, D) Urethral calibers of the experimental groups 4 and 24 weeks after the procedure, respectively. (E) The mean urethral diameters of the normal, stricture, and experimental groups B (4 weeks) and D (24 weeks). (F) The asterisk indicates a significant difference ( $P < .05$ ) in the urethral diameter of the experimental and normal groups compared with that of the stricture group. The pound sign indicates no statistically significant difference ( $P > .05$ ) in the normal group vs the experimental group. “n.s.” indicates no statistically significant difference ( $P > .05$ ) in experimental group B versus experimental group D. The white arrow indicates the stricture.

## COMMENT

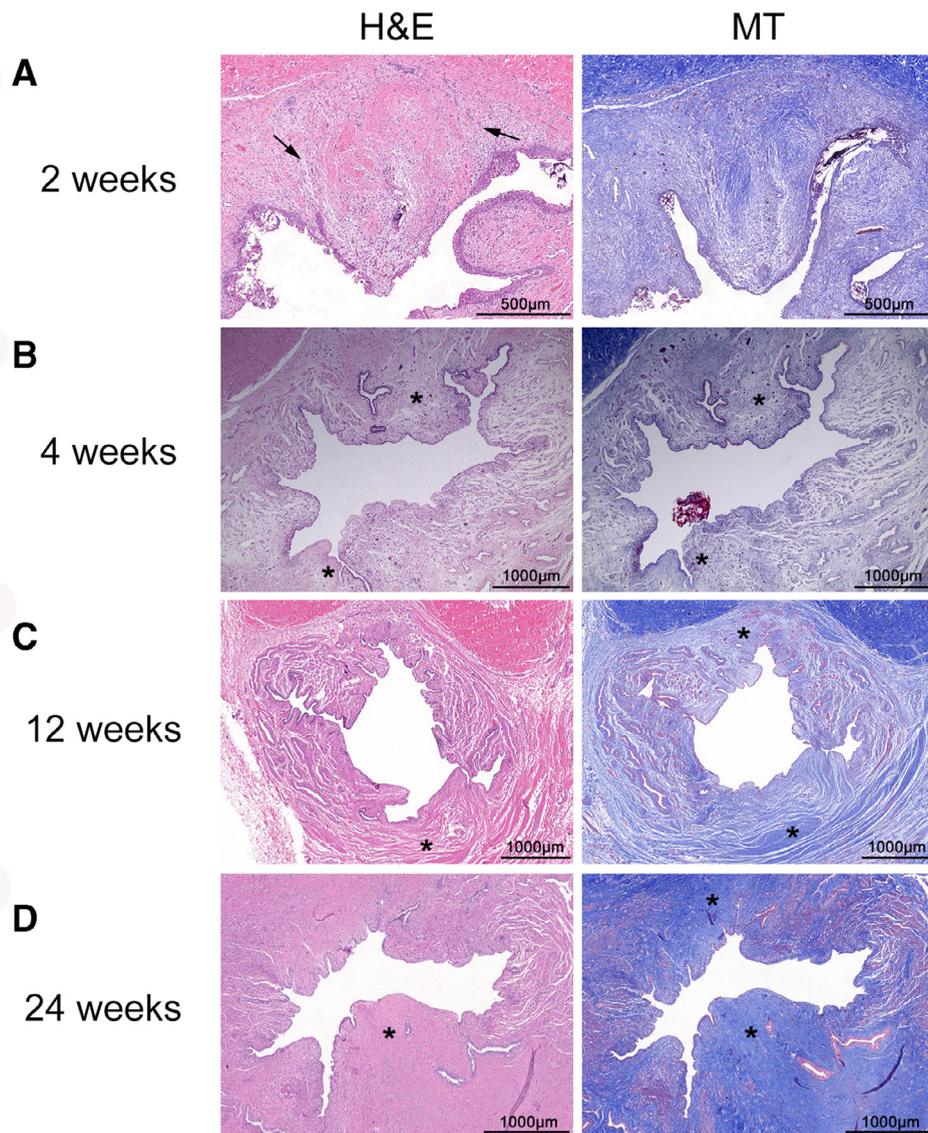
Substitution urethroplasty is an effective therapeutic technique for complicated or multioperated urethral stricture. Various substitution materials are available, including a preputial graft,<sup>6</sup> full-thickness skin graft,<sup>7</sup> oral mucosa,<sup>8</sup> bladder mucosa,<sup>9</sup> tunica vaginalis,<sup>10</sup> and colonic mucosa.<sup>11</sup> Skin grafts are frequently used as materials in urethral reconstruction when available. However, they have a potential risk of contracture and hair growth in the urethra and are insufficient in quantity due to previous failed urethral surgeries or circumcision.<sup>18</sup> The bladder mucosa has been associated with many complications, including meatal stenosis, prolapse, and fistula.<sup>9</sup> The colonic mucosa, which is suitable for long urethral strictures, has been reported to have good results.<sup>11</sup> However, collecting this material involves a highly invasive procedure and has the potential complications of abdominal surgery.

The oral mucosa is the most widely used material in the clinic and has been proven to be an ideal tissue substitute. Numerous clinical studies using oral mucosa for substitution urethroplasty have yielded high success rates.<sup>8,19</sup> To date, the oral mucosa is recommended as the first choice

and is likely to become the gold standard for substitution urethroplasty.<sup>12</sup>

However, harvesting the oral mucosa carries a risk of morbidity of the donor site, such as postoperative infection, pain, swelling, damage to the parotid duct, and limitation of oral opening.<sup>12</sup> Wood et al<sup>20</sup> evaluated the morbidity of buccal mucosa grafts harvested for urethroplasty in 57 patients. Of these patients, 83% developed postoperative pain, 68% had perioral numbness that persisted after 6 months in 26% of the patients, 67% initially had difficulty with mouth opening that persisted after 6 months in 9% of the patients, and 2% had a mucous retention cyst. Dublin et al<sup>21</sup> reported that 57% of patients had oral numbness after surgery (during the first 48 hours) that persisted for a year in 16% of patients and that 75% of patients complained of tightness of the mouth after surgery (during the first 48 hours) that persisted for nearly 2 years in 32% of cases. Meanwhile, the sources of substitution material for a long and complicated urethral stricture are limited.<sup>13</sup>

In our study, we chose a tunica vaginalis graft as a substitution material for urethroplasty. The reason we used the tunica vaginalis graft was that, compared to oral



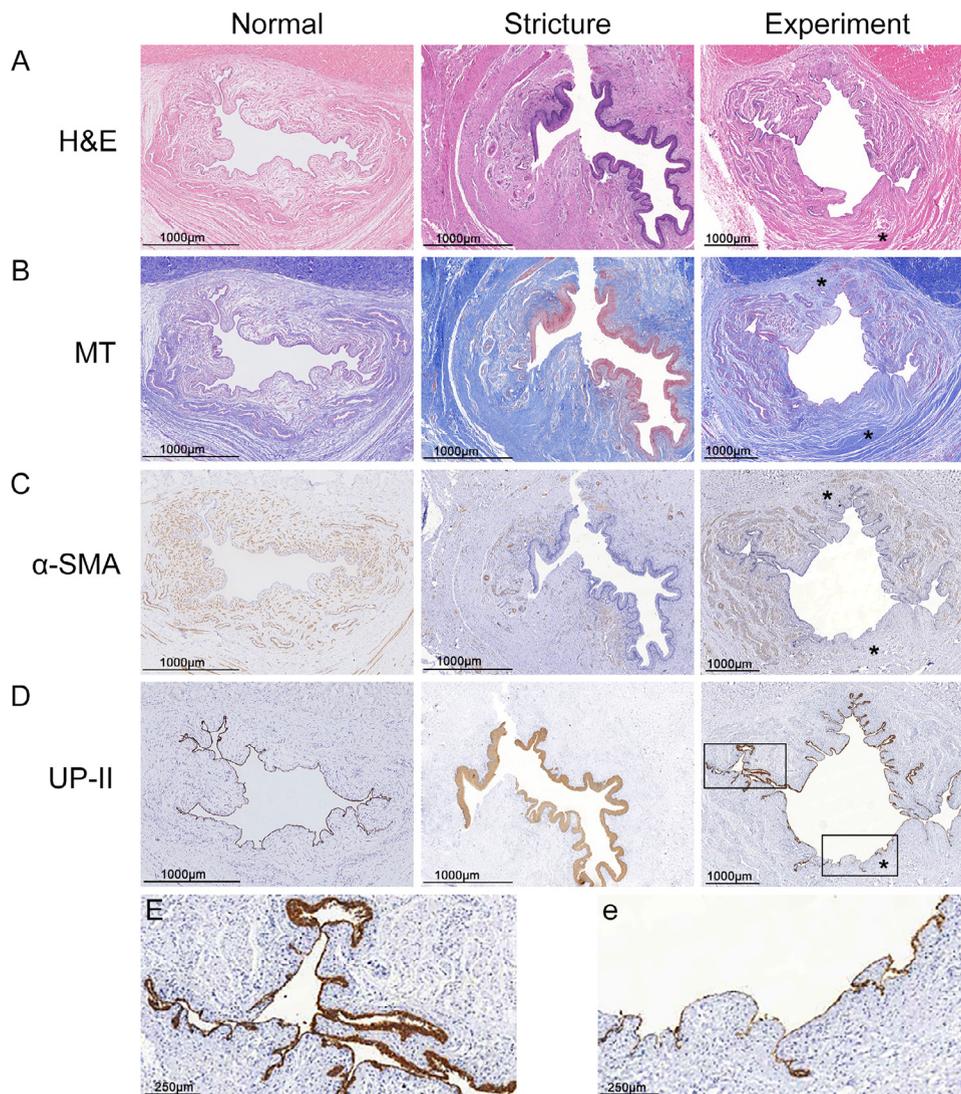
**Figure 3.** Histological analysis of the urethra in the experimental group at different periods. (A) Hematoxylin and eosin staining showed that the tunica vaginalis graft survived and the transition area between the normal urethra and tunica vaginalis graft could be discerned. Masson's trichrome staining showed that the submucosal collagen bundles of the tunica vaginalis graft had a connection with those of the normal urethra. (B) The tunica vaginalis graft completely integrated in the urethra. (C) Hematoxylin-eosin-stained sections showed that the tunica vaginalis graft covered the pseudostratified epithelium. Masson's trichrome-stained sections showed that the orientation of the collagen bundles in the tunica vaginalis graft region resembled those in the normal urethra. (D) The epithelium was intact, and the structure of the tunica vaginalis graft could barely be discerned. However, the smooth muscle fibers were sparse in the position of the tunica vaginalis graft. Black arrows indicate the transition area. The asterisks indicate the tunica vaginalis graft. (Color version available online.)

mucosa, it could be easily harvested and involved almost no additional injury to the donor site. This choice may decrease the operative time and reduce donor site morbidity. Moreover, the tunica vaginalis material is abundant in quantity, which is essential for a long and multioperated urethral stricture. Many studies have confirmed the survival of tunica vaginalis grafts and have verified the transformation of this material into urinary epithelium when placed in the urinary tract.<sup>15,16,23</sup>

Experimental studies in urethral reconstruction using tunica vaginalis tissue in both the dorsal onlay<sup>15,22</sup> and

ventral onlay procedures<sup>23</sup> acquired good results. Theodorescu et al<sup>16</sup> compared the use of the tunica vaginalis for urethroplasty in both a tube flap and an onlay flap in rabbits. All rabbits that underwent tunica vaginalis tube flap reconstruction resulted in stenosis, while no stenosis occurred in the onlay flap group. Thus, the tunica vaginalis may be better used as a patch-type graft rather than a tubular-type graft.

Clinical application of tunica vaginalis tissue for urethral reconstruction has also obtained encouraging results.<sup>10,14</sup> Foinquinos et al<sup>14</sup> performed urethroplasty



**Figure 4.** Histological and immunohistochemical (IHC) analyses of the urethra in the different groups. (A) Hematoxylin-eosin staining showed a narrow urethral lumen with deficient epithelial layers in the stricture group. (B) Masson's trichrome staining showed severe fibrosis with irregularly arranged collagen bundles in the stricture group. (C) IHC analysis with the anti-alpha smooth muscle actin antibody showed abundant smooth muscle layers and richly endowed vessels in the experimental group compared with those of the stricture group. (D) IHC analysis with the UP-II antibody targeting the urothelium showed an intact urothelial layer. The native urethra showed a covered stratified urothelial lining (E). The tunica vaginalis graft was replaced by a pseudostratified uroepithelial lining (e). The asterisks indicate tunica vaginalis graft. (Color version available online.)

with a dorsal tunica vaginalis graft in 11 patients and had a 100% urethral patency rate at the 5-month follow-up. Mathur and Sharma<sup>10</sup> performed tunica vaginalis urethroplasty in 86 patients and had an 89.5% success rate at the end of the 36-month follow-up.

Currently, the published techniques for both dorsal onlay urethroplasty and ventral onlay urethroplasty may not create an adequate lumen for a very tight anterior urethral stricture containing obliterative or nearly obliterative sections.<sup>5,24,25</sup>

To solve this issue, Palminteri et al<sup>5</sup> first performed urethroplasty using combined dorsal plus ventral double buccal mucosa grafts and obtained encouraging results.

Subsequently, several studies that used the Palminteri technique for both penile and bulbous strictures also obtained good results.<sup>13,24,26,27</sup> In 2012, Palminteri et al<sup>28</sup> performed a study comparing the results of 3 different surgical techniques for urethroplasty in dorsal onlay, ventral onlay, and dorsal plus ventral onlay and confirmed equivalent effects among the 3 surgical techniques.

The use of a dorsal plus ventral onlay graft to augment the urethral plate has been described using penile skin or buccal mucosa. In our study, we used an original technique with tunica vaginalis grafts. The dorsal graft is anchored to the corpora cavernosa, which offers a vascular bed and improves the chance of neovascularization. The

ventral graft is supported by the abundant ventral spongiosum, which can facilitate graft survival. Furthermore, by reducing the width of the single ventral graft, the Palminteri technique may reduce the possibility of fistulas and diverticulum. This technique also preserves the integrity of the urethral vascularity and the urethral length, which may reduce sexual complications.<sup>29</sup>

In our study, all animals in the experimental group showed a patent urethra 4 weeks and 24 weeks after the procedure, as evidenced by radiology, demonstrating that the short-term and long-term effects of this technique were encouraging. The explanation for our good results is probably that double tunica vaginalis grafts are well supported by their own independent vascular bed, which can aid in graft survival. Moreover, we observed the transformation of the tunica vaginalis mesothelium into urothelium, as evidenced by IHC analysis with the UP-II antibody, which was used for the identification of urothelium, not mesothelium. The covering epithelial lining in the grafting region of the tunica vaginalis was homogeneous, demonstrating that the change from the mesothelium to urothelium resulted from a metaplasia alteration rather than migration of the peripheral urothelium. This alteration is consistent with reports in other publications.<sup>15,16,22</sup>

Although the results of our study are encouraging, our study has limitations. We performed no further comparative analysis of the efficacy between the tunica vaginalis graft and buccal mucosa graft using the same technique. Further studies are needed prior to clinical application of this technique.

## CONCLUSION

Combined dorsal plus ventral double tunica vaginalis graft urethroplasty can be successfully used for urethral reconstruction in a rabbit model. The tunica vaginalis graft can survive in the urinary tract and transform into a urinary pseudostratified epithelium to maintain urethral patency. However, further studies are needed prior to clinical application of this technique.

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## EDITORIAL COMMENT

In recent decades, oral mucosa grafts have increasingly replaced flaps and other grafts in the reconstructive urologists' armamentarium for repair of urethral strictures by substitution urethroplasty. With the rise in oral mucosa graft use, there has also been a greater consideration of the potential limitations and morbidity of oral mucosa graft harvesting.<sup>1</sup> As a result, further alternative graft sources have been investigated. Tunica vaginalis has been proposed as a potential alternate graft source for substitution urethroplasty, with several animal model studies and a small series of patients showing promising results in the short term.<sup>2,3</sup> Tunica vaginalis may present some advantages over oral mucosa grafts, including its ease of harvest, lack of morbidity, and larger surface area.

The authors here present an experimental rabbit model study applying tunica vaginalis grafts to substitution urethroplasty with a combined dorsal inlay and ventral onlay approach. The authors showed histologically that with time the mesothelial layer of the tunica vaginalis transformed into urothelium. Radiographically, the experimental groups also showed similar patency of the urethra at the conclusion of the study as compared to the normal controls. These promising results provide additional support for tunica vaginalis grafts as another potential source of graft material for the reconstructive urologist. In particular, tunica vaginalis grafts may be useful in long segment strictures or recurrent strictures after failed prior oral mucosa graft urethroplasty. The authors also note that by performing a combined approach with a dorsal inlay and a narrower ventral onlay graft, concerns of sacculation, or diverticulum formation with tunica vaginalis grafting may be mitigated.

This animal model study highlights the potential application and promise of tunica vaginalis grafting, but also illustrates how far away from widespread clinical use it is. Questions about the long-term success and potential pitfalls of tunica vaginalis graft urethroplasty in humans remain unknown. Without a doubt, further clinical studies in humans are needed; yet this study does present a thoughtful possibility for reconstructive urologists to consider going forward.

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## AUTHOR REPLY

The use of oral mucosa grafts is the best available option for substitution urethroplasty and the high success rate of the procedure has obtained despite the graft position.<sup>1</sup> However, the search for other substitution materials available is still active and the tunica vaginalis is one of substitution materials which has been used.<sup>2</sup>

For a very tight anterior urethral stricture, the augmented anastomotic urethroplasty has been proposed as an option to increase the results of substitution urethroplasty. But, the augmented anastomotic urethroplasty has limits regarding the length of the stricture.<sup>3</sup> Moreover, increasing the graft or flap width is another option, which can increase the risk of fistulas and diverticulum. To best solve the discrepancy, the procedure of a combined ventral onlay and dorsal inlay graft has been performed.<sup>4</sup>

In our study, we first introduced the bleomycin injection technique to create an animal model of urethral stricture,<sup>5</sup> and then performed urethroplasty using combined dorsal plus ventral double tunica vaginalis grafts. The encouraging results were obtained, evaluated by retrograde urethrography, and histological analysis at different time points, suggesting the procedure can be another option for urethral reconstruction. Though the procedure of a combined dorsal plus ventral double tunica vaginalis graft urethroplasty is promising, we must emphasize that further studies are needed to evaluate longer term success rate prior to clinical application of this technique.

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