Third Prize

Ureteral Tissue Balloon Expansion for Laparoscopic Bladder Augmentation: Survival Study

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ABSTRACT

Background and Purpose: The search for the perfect urinary bladder substitute continues. Despite their inherent limitations, intestinal segments remain the commonest material for bladder reconstruction. The ureter, with its transitional epithelium, may be the ideal tissue to augment the bladder. Ikekuchi et al reported the feasibility of chronic ureteral balloon expansion by open surgery (J Urol 1998;159:1665). Herein, we propose a completely minimally invasive approach to balloon overdistend a segment of juxtavesical ureter incrementally and to use this in-line tissue-expanded ureteral patch to augment the bladder laparoscopically.

Materials and Methods: In five female pigs, a novel ureteral expansion balloon device (Microvasive, MA) was inserted percutaneously and advanced antegrade into the juxtavesical ureter. The device has two channels: one for balloon inflation and the other for draining the kidney. After progressive ureteral expansion over a 3- to 4-week period, laparoscopic augmentation ureterocystoplasty was performed. Animals were euthanized at 15 days (N = 1), 1 month (N = 1), 2 months (N = 1), and 3 months (N = 2).

Results: Percutaneous balloon device placement was technically successful in all five cases (mean operating room time 52 minutes). The mean volume of the tissue-expanded ureter at 1, 2, and 3 weeks was 12.9 cc, 60.3 cc, and 171.8 cc, respectively. Laparoscopic augmentation ureterocystoplasty with (N = 3) or without (N = 2) concomitant subtotal cystectomy was technically successful in all five cases without any open conversion. The mean operative time was 126.5 minutes, and the mean blood loss was 29 mL. Postoperative complications consisted of one case each of pyelonephritis and ureteral stricture. At autopsy, the mean capacity of the bladder was 574 mL, and the Pves at maximum capacity was 14 cm H2O. Histologic examination of the tissue-expanded ureter revealed regenerated transitional epithelium and muscle hypertrophy.

Conclusions: Chronic ureteral tissue expansion can be carried out safely and efficaciously. The expanded tissue is thick, healthy, and vascular, with histologic features of normal transitional epithelium and muscle hypertrophy and hyperplasia. This expanded ureteral tissue can be used to augment the bladder with laparoscopic techniques. Such augmented bladders do not show significant shrinkage and possess urodynamic characteristics of normal capacity and normal compliance over a follow-up of 3 months.
INTRODUCTION

Augmentation cystoplasty is indicated in a variety of disease states that reduce the capacity or compliance of the bladder. Currently, various intestinal segments are the tissue substitutes most frequently used for this purpose clinically. The disadvantages of using intestinal segments in urinary tract reconstruction include bone and metabolic changes, mucus production, and tumor formation. These disturbances may be exaggerated in patients with compromised renal function and in children.

The ureter, with its transitional epithelium, may be an excellent tissue for bladder augmentation with good long-term urodynamic properties and minimal metabolic alterations. Currently, the clinical use of ureterocystoplasty is limited to the occasional patient with a megaureter and nonfunctioning ipsilateral kidney.

Tissue expansion has been used successfully to increase the surface area of skin grafts in patients with burns. Tissue expansion has also been utilized experimentally in urinary tract reconstruction, with promising early results. In this study, we assessed the feasibility and efficacy of chronic progressive expansion of the normal juxtavesical ureter using a novel percutaneously inserted balloon and subsequent application of the tissue to laparoscopic augmentation of the bladder in a survival porcine model.

MATERIALS AND METHODS

The study was performed in 35- to 40-kg female farm pigs, after approval from the Animal Research Committee of our institution in accordance with the Guide for the Care and Use of Laboratory Animals, National Research Council 1996. The initial five animals were used to develop the prototype design and insertion technique of the ureteral expansion balloon, its inflation schedule, and the technique of laparoscopic ureterocystoplasty. Subsequently, five animals entered the survival study.

Percutaneous insertion of ureteral expansion balloon

All five chronic animals underwent unilateral (right three, left two) percutaneous insertion of the ureteral expansion balloon (Microvasive, Natick, MA), a dual-channel balloon catheter: one for inflation, and the other for proximal nephrostomy drainage (Fig. 1). Initially, a 5F open-ended ureteral catheter was inserted cystoscopically into the ipsilateral renal collecting system. The animal was then positioned prone, and percutaneous renal access was obtained under fluoroscopic guidance. A 0.035-inch Glide-wire (Microvasive) was manipulated antegrade down the ureter and retrieved through the bladder, and

![FIG. 1. Ureteral expansion was performed using novel silicone balloon catheter having two channels: a smaller one to inflate balloon and a larger fenestrated one to drain kidney. Catheter has 14F shaft with multiple holes to facilitate proximal urinary drainage. Balloon (b) has maximal capacity of 600 mL and has radiopaque markers (m₁ and m₂) at both ends to facilitate fluoroscopic observation during placement. Additional radiopaque marker (m₃) on shaft immediately proximal to last drainage hole should lie within kidney. Terminal end of catheter is fashioned into pigtail to facilitate retention in bladder. Single-step dilator (d) is used to position 20F peel-away sheath (s) within renal collecting system.](image)

![FIG. 2. Diagram of initial procedure. (A) percutaneous insertion of ureteral expansion device. Peel-away sheath is seen in renal pelvis, with balloon just beyond ureteropelvic junction. (B) Final balloon position. (Right) Deflated balloon is positioned in juxtavesical ureter. (Left) Incremental progressive inflation of balloon causes expansion of juxtavesical ureter.](image)
the open-ended ureteral catheter was removed. Using an antegrade 5F ureteral catheter, the Glide-wire was replaced with a 0.035-inch Amplatz Superstiff guidewire (Microvasive). The percutaneous tract was dilated using a single-step dilator, and a 20F peel-away sheath was positioned in the renal pelvis. A 21F 10-cm ureteral dilation balloon (Uromax; Microvasive) was used to dilate the entire ureter in a step-wise fashion over a period of 2 minutes to facilitate subsequent passage of the novel expansion device.

The adequately lubricated balloon expansion catheter was gradually manipulated antegrade into the ureter over the Superstiff guidewire (Fig. 2A). The balloon, flanked by radiopaque markers, was positioned in the juxtavesical ureter and distended with 2.5 to 3 mL of contrast medium to secure it in position (Fig. 2B). The excess proximal length of the catheter exiting the animal’s back was tunneled subcutaneously so that only the inflation and drainage ports were visible outside the skin.

**Chronic ureteral expansion**

Starting the day after placement of the ureteral expansion balloon, the ureter was gradually dilated by daily incremental instillation of a dilute (1:4) contrast solution. The inflation was carried out without anesthesia or analgesia while the overnight-fasting animal was busily eating. Ureteral expansion was monitored radiologically every 7 to 10 days (Fig. 3).

**Laparoscopic augmentation ureterocystoplasty**

Laparoscopic ureterocystoplasty was performed in all five animals after 3 to 4 weeks of ureteral expansion. All procedures were performed using a four-port transperitoneal approach with the pig under general anesthesia. Initially, the ureteral balloon was completely deflated, and the amount of fluid aspirated was measured. The balloon was subsequently refilled with the same amount of dilute antibiotic solution to facilitate intraoperative identification and prevent intraoperative spillage of potentially infected fluid should inadvertent puncture of the balloon occur intraoperatively.

After port placement, the pelvic organs were examined laparoscopically. The expanded ureter was identified as a readily visible bulge adjacent to the urinary bladder. The medial peritoneum overlying the expanded ureter was incised to expose the ureteral wall. The fallopian tube and ovary on the ipsilateral side were mobilized away from the ureter. The bladder was mobilized by dividing the medial umbilical ligament and the superior vesical pedicle and incised laterally in a longitudinal fashion from just above the ureteral orifice up to the dome. The ureteral orifice and intramural ureter were preserved. Whereas in the initial two animals, the bladder dome was not excised, in the latter three, approximately 80% of the bladder was removed. The medial wall of the expanded ureteral segment was then incised using a J-hook monopolar cautery electrode, thus opening the expanded ureteral segment medially. Care was taken to minimize any mobilization of the ureter, thus maintaining intact the laterally based vascularity of the expanded ureter (Fig. 4). The length, site, and orientation of the ureteral incision was tailored to correspond to the bladder defect (Figure 5).

After the ureteral incision was completed, the balloon was deflated and the catheter removed. The in-line tissue-expanded ureteral patch was then anastomosed to the bladder in a running fashion using 2-0 Vicryl sutures on a CT-1 needle with freehand intracorporeal laparoscopic suturing and knot-tying techniques (Fig. 6). After the posterior wall was sutured, an 18F red rubber urethral catheter was inserted antegrade into the urethra through the bladder neck. The anterior wall was then sutured to complete the augmentation ureterocystoplasty. A 22F Malecot suprapubic catheter was left indwelling and brought out through the suture line in the initial two animals only. A

**FIG. 3.** Plain radiographs of abdomen document progressive ureteral expansion. (A) At 1 week with 12-mL volume. (B) At 2 weeks, volume in balloon has increased to 46 mL. (C) At 25 days just prior to augmentation ureterocystoplasty with 140 mL in balloon.
22F tube drain was positioned in the prevesical space in all five animals and brought out through a port site. The animals were returned to the chronic animal care facility.

Follow-up

Oral antibiotics were administered until urethral catheter removal. The suprapubic catheter was removed after 7 days, and the urethral catheter was removed after 14 days if not spontaneously expelled earlier. The drain, if not spontaneously expelled, was removed a day after the urethral catheter was removed. All animals underwent laboratory, radiologic, urodynamic, and histologic investigations (Table 1). Additionally, transmission electron microscopy of the expanded ureter and measurement of vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β2 in expanded ureteral tissue were performed in selected animals. Animals were euthanized at 15 days (N = 1), 1 month (N = 1), 2 months (N = 1) and 3 months (N = 2).

RESULTS

Percutaneous insertion of ureteral expansion balloon

Percutaneous insertion was technically successful with satisfactory balloon placement in all five animals. The mean operative time required for balloon insertion was 52 ± 10.6 minutes, and there were no complications (Table 2).

Chronic ureteral expansion

All five animals underwent successful ureteral expansion over a mean of 25 ± 1.4 days (Table 3). The mean final volume of the ureter was 177.1 ± 41.3 mL. The mean volume of fluid instilled was 12.7 ± 0.9 mL in the first week, 38.4 ± 4.3 mL in the second week, 66.2 ± 17.4 mL in the third week, and 59.8 ± 28.4 mL in the fourth week. The mean daily inflation volume was 1.8 ± 0.1 mL in the first week, 5.5 ± 0.6 mL in the second week, 11.3 ± 2.5 mL in the third week, and 16.1 ± 1.8 mL in the fourth week.

All five awake animals readily tolerated the daily incremental instillation of dilute contrast solution without apparent pain or discomfort. The ureteral expansion balloon did not malfunction in any case, as judged by leakage of fluid, blockage of the channel, balloon migration, or rupture. Radiologic volumetric assessment of the ureteral balloon during the phase of ureteral expansion was commensurate with the amount of fluid instilled. We did not note any complications during ureteral expansion. Proximal urinary drainage through the fenestrated channel of the ureteral expansion catheter was adequate in all five animals.

Laparoscopic augmentation ureterocystoplasty

Laparoscopic ureterocystoplasty was technically successful in all five animals without need for open conversion in any case. The mean operative time was 156 ± 41.1 minutes (range 115–210 minutes), and the mean estimated blood loss was 29 ± 16 mL (range 10–50 mL). One animal had a small-bowel serosal tear, which was readily suture repaired laparoscopically.

Some periureteral adhesions were encountered in the vicinity of the expanded ureter, which could readily be lysed laparoscopically. Intraoperatively, at the time of ureterocystoplasty, the expanded ureter appeared thick and highly vascular, with areas of urothelial denudation. Intraoperative instillation of saline through the urethral catheter at the end of the ureterocystoplasty revealed a watertight anastomosis in all five cases. Postoperative complications were seen in two animals: lower ureteral obstruction and pyelonephritis with urosepsis.

Urodynamic, cystography, and cystoscopy data

Over a follow-up ranging from 15 days to 3 months, the mean bladder capacity was 574 ± 221.3 mL (range 380–940 mL). The $P_{ves}$ at maximum capacity was 14 ± 4.5 cm H$_2$O (range 8–20 cm H$_2$O), and bladder compliance was 71.7 mL/cm H$_2$O (range 35.3–188 mL/cm H$_2$O). Uninhibited detrusor contractions were not evident on urodynamic evaluation in any of the five animals (Table 4).

Cystography revealed ipsilateral reflux in four renal units: grade II in one animal, grade IV in two animals, and grade V in one animal (Fig. 7). At autopsy, one renal unit demonstrated lower-ureteral obstruction and therefore showed no reflux on cystography. There was no contralateral reflux in any renal unit. In all four refluxing units, the refluxed contrast drained from the kidney immediately after the bladder was emptied, thereby ruling out any ureteral obstruction. Additionally, the cystogram did not reveal contrast extravasation in any case.
**FIG. 5.** Diagram (A) and intraoperative photograph (B) show opened bladder (b) and expanded ureter (u). Deflated expansion balloon (arrow) is collapsed within lumen of expanded ureteral segment. Notice that thickness of wall of expanded ureter is almost equal to that of native bladder.

**FIG. 6.** Laparoscopic augmentation ureterocystoplasty. (A) Diagram and (B) intraoperative photograph showing ureterocystoplasty in progress. Posterior anastomosis between expanded ureter (u) and bladder (b) has been almost completed. (C) Diagram and (D) intraoperative photograph of completed ureterocystoplasty. Bladder (b) and expanded ureteral (u) patch have been anastomosed.
Cystoscopy was performed in all animals at 1 month and at autopsy. By 1 month, the bladder revealed a fully regenerated mucosa in four animals; one animal euthanized at 15 days still had patchy areas of denuded mucosa.

**Laboratory data**

Laboratory examination revealed minimal metabolic alterations in four animals. One animal that developed pyelonephritis and urosepsis had evidence of azotemia, hyponatremia, hyperkalemia, and acidosis (Table 5). The mean serum creatinine concentration was 1.3 ± 0.2 mg/dL at baseline, 0.9 ± 0.2 mg/dL at bladder augmentation, and 2.0 ± 0.9 mg/dL at euthanasia.

**Autopsy data**

At autopsy, the ureteral patch appeared well vascularized, and the ureterocystoplastysuture line was healed in all five animals (Fig. 8). The ipsilateral renal parenchyma appeared grossly normal in three cases, with pre-euthanasia intravenous urography (IVU) revealing prompt opacification with mild hydronephrosis. One animal with a lower ureteral obstruction revealed thinning of parenchyma and poor function on IVU. At autopsy, the obstruction was found to be the result of flimsy synechia formation at the junction where the upper, normal-caliber, ureter entered the expanded ureteral segment. The animal with pyelonephritis and urosepsis had a grossly scarred kidney that was nonfunctioning on IVU.

**Histologic data**

Light microscopic examination of biopsies of the expanded ureter revealed muscle hypertrophy and hyperplasia, mucosal atrophy, and variable inflammatory infiltrate. Histologic examination of the expanded ureter harvested at the time of autopsy revealed persistent muscle hypertrophy and hyperplasia, a fully regenerated transitional epithelium, and variable amount of fibrosis (Fig. 9).

**Electron microscopic data**

Transmission electron microscopy performed on the ureteral tissue obtained at the time of laparoscopic augmentation revealed cellular evidence consistent with muscular hypertrophy and hyperplasia (Fig. 10).

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**Table 1. Investigation Schedule**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Laboratory: complete blood count, metabolic profile, urinanalysis and culture</th>
<th>Prior to balloon insertion</th>
<th>Prior to augmentation ureterocystoplasty</th>
<th>Prior to euthanasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>Radiologic</td>
<td>Weeklly during balloon inflation</td>
<td>Prior to augmentation ureterocystoplasty</td>
<td>At 1-month follow-up</td>
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<tr>
<td>Timing</td>
<td>Cystogram</td>
<td>At 1-month follow-up (N = 2)</td>
<td>Prior to euthanasia</td>
<td>Prior to euthanasia</td>
</tr>
<tr>
<td>Timing</td>
<td>Intravenous urogram</td>
<td>Prior to euthanasia</td>
<td>Prior to euthanasia</td>
<td>Prior to euthanasia</td>
</tr>
<tr>
<td>Timing</td>
<td>Urodynamics</td>
<td>At 1-month follow-up (N = 2)</td>
<td>Prior to euthanasia</td>
<td>Prior to euthanasia</td>
</tr>
<tr>
<td>Timing</td>
<td>Cystoscopy</td>
<td>Prior to balloon insertion</td>
<td>Prior to augmentation ureterocystoplasty</td>
<td>Prior to euthanasia</td>
</tr>
<tr>
<td>Timing</td>
<td>Histology</td>
<td>During augmentation cystoplasty</td>
<td>At euthanasia</td>
<td>During augmentation cystoplasty (N = 2)</td>
</tr>
<tr>
<td>Timing</td>
<td>Light microscopy</td>
<td>During augmentation cystoplasty (N = 2)</td>
<td>At euthanasia</td>
<td>During augmentation cystoplasty (N = 5)</td>
</tr>
<tr>
<td>Timing</td>
<td>Transmission electron microscopy</td>
<td>During augmentation cystoplasty (N = 2)</td>
<td>At euthanasia</td>
<td>During augmentation cystoplasty (N = 5)</td>
</tr>
<tr>
<td>Timing</td>
<td>Tissue cytokine assay (VEGF and TGF-β2)</td>
<td>During augmentation cystoplasty (N = 5)</td>
<td>At euthanasia</td>
<td>During augmentation cystoplasty (N = 5)</td>
</tr>
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*Seven tissue biopsies were obtained from the five animals at the time of augmentation ureterocystoplasty for cytokine assay.

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**Table 2. Intraoperative Data**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Mean time for balloon insertion (min) 52 ± 10.6 (39–68)</th>
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</thead>
<tbody>
<tr>
<td>Timing</td>
<td>Mean time for bladder augmentation (min) 156 ± 41.1 (115–210)</td>
</tr>
<tr>
<td>Timing</td>
<td>Estimated blood loss (mL) 29 ± 16 (10–50)</td>
</tr>
<tr>
<td>Timing</td>
<td>Subtotal cystectomy performed (N) 3</td>
</tr>
<tr>
<td>Timing</td>
<td>Ureteral stenting (N) 2</td>
</tr>
<tr>
<td>Timing</td>
<td>Urethral catheter (N) 5</td>
</tr>
<tr>
<td>Timing</td>
<td>Suprapubic catheter (N) 4</td>
</tr>
<tr>
<td>Timing</td>
<td>Open conversion (N) 0</td>
</tr>
<tr>
<td>Timing</td>
<td>Intraoperative complications (N) Serosal bowel tear repaired</td>
</tr>
<tr>
<td>Timing</td>
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</tbody>
</table>

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Growth factor assay

Preliminary data on growth factor expression in expanded ureteral tissue obtained and snap frozen at the time of augmentation ureterocystoplasty revealed a twofold to threefold increase in TGF-β2 (median 44 pg/mL; range 27–49 pg/mL) over controls (normal ureter 16 pg/mL) (Table 6). There was no increase in VEGF expression in the expanded ureteral tissue compared with control samples.

DISCUSSION

The search for the ideal tissue substitute for bladder augmentation is ongoing. Currently, intestinal segments remain most commonly used for bladder augmentation. Although the results of augmentation cystoplasty using various bowel segments have generally been acceptable, these tissues are associated with absorptive metabolic changes, mucus production, and...
stone formation, the magnitude of which is dependent on the length and segment of bowel used.\(^2\)

Significant research in the past few decades has focused on alternative tissue substitutes for urinary tract reconstruction. These have included tissue-engineered materials,\(^7\) xenografts such as small-intestinal submucosa (SIS),\(^8\) and techniques such as autoaugmentation\(^9\) and deepithealized bowel.\(^10\) Some of these techniques, although promising, have either been insufficiently durable or require considerable refinement.

The ureter, with its transitional epithelium, is potentially an optimal tissue for bladder augmentation.\(^3\) Augmentation ureterocystoplasty has been reported, with encouraging long-term urodynamic results, and limited, if any, metabolic changes. However, the amount of ureteral tissue needed to provide a urodynamically acceptable bladder augmentation can be obtained only in a patient with a large megaureter. Therefore, currently, augmentation ureterocystoplasty is limited to the occasional patient with a megaureter and a nonfunctioning kidney who requires bladder augmentation.

Tissue expansion techniques have been employed successfully in various areas of medicine such as breast reconstruction, craniofacial surgery, and plastic reconstructive surgery in patients with extensive burns.\(^4\) Studies with chronic skin expansion have shown that tissue expansion is not simply a physical stretching of tissues but a complex biologic phenomenon involving interplay of various cytokines and growth factors. Takei and colleagues\(^11\) reviewed the molecular events underlying chronic stretching of the skin and concluded that the increase in the surface area after chronic expansion is a result of generation of new skin and not simply a stretching of the preexpansion skin. The cell growth associated with mechanical stretch is thought to be induced by a complex interplay of growth factors and membrane-bound molecules.

Tissue expansion techniques have also been utilized experimentally in urinary tract reconstruction. Lailas and colleagues\(^5\) initially reported chronic ureteral expansion for subsequent ureterocystoplasty. Ten rabbits underwent ligature of the ipsilateral ureter near the ureterovesical junction. The proximal ureter was transected and anastomosed to the opposite ureter as a transureteroureterostomy, and the distal ureter was brought out through the skin via a silicone catheter for chronic expansion. The ureter was progressively expanded, and augmentation ureterocystoplasty was subsequently performed using the dilated ureteral segment. The authors reported an average increase in bladder capacity of 260%.

Ikeguchi and associates\(^1\) performed chronic segmental ureteral expansion in a porcine model. The tissue expander consisted of a latex balloon attached to a catheter and was implanted by open surgery. A separate nephrostomy tube was placed to provide urinary drainage of the ipsilateral renal unit. The pigs underwent daily ureteral dilation over a period of 2 to 4 weeks (volume range 150–1000 mL) and subsequent open surgical ureterocystoplasty. The authors reported an increase in bladder capacity, which remained consistent over the follow-up period.

Thus, although the potential for ureteral tissue expansion for urinary tract reconstruction has been demonstrated, further characterization of the biology of ureteral expansion and refinement of technique are necessary prior to its clinical application. Our study was designed specifically to address the following cru-

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**Table 5. Serum Biochemical Data**

<table>
<thead>
<tr>
<th></th>
<th>Prior to ureteral balloon expansion</th>
<th>Prior to augmentation cystoplasty</th>
<th>Prior to euthanasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean serum creatinine (mG/dL)</td>
<td>(1.3 \pm 0.2) (1.1–1.4)</td>
<td>(0.9 \pm 0.2) (0.7–1.1)</td>
<td>(2.0 \pm 0.9) (1.4–3.4)</td>
</tr>
<tr>
<td>Mean serum potassium (mEq/L)</td>
<td>(139.4 \pm 3.3) (136–143)</td>
<td>(135.5 \pm 7.0) (127–144)</td>
<td>(132.5 \pm 9.7) (119–140)</td>
</tr>
<tr>
<td>Mean serum sodium (mEq/L)</td>
<td>(4.3 \pm 0.2) (4.1–4.5)</td>
<td>(4.4 \pm 0.2) (4.1–4.6)</td>
<td>(4.7 \pm 0.6) (4.1–5.4)</td>
</tr>
<tr>
<td>Mean serum chloride (mEq/L)</td>
<td>(97.2 \pm 3.4) (93–102)</td>
<td>(95.5 \pm 6.5) (88–103)</td>
<td>(88 \pm 18.9) (66–100)</td>
</tr>
<tr>
<td>Mean serum carbon dioxide (mEq/L)</td>
<td>(27 \pm 3.3) (24)</td>
<td>(27.8 \pm 0.5) (27–28)</td>
<td>(24 \pm 5.7) (16–19)</td>
</tr>
<tr>
<td>Mean anion gap</td>
<td>(15.2 \pm 3.9) (9–19)</td>
<td>(12.3 \pm 1.0) (11–13)</td>
<td>(18.3 \pm 11.4) (10–35)</td>
</tr>
<tr>
<td>Mean hemoglobin (mg/dL)</td>
<td>(11.6 \pm 0.3) (11.3–12)</td>
<td>(9.6 \pm 1.0) (8.7–10.9)</td>
<td>(10.3 \pm 2.6) (8.8–14.1)</td>
</tr>
<tr>
<td>Mean hematocrit (%)</td>
<td>(39.8 \pm 2.0) (37.7–42.3)</td>
<td>(32.0 \pm 3.4) (29.1–35.8)</td>
<td>(35.3 \pm 8.1) (27.7–46.8)</td>
</tr>
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</table>
special issues: (1) the feasibility of percutaneous insertion of the ureteral expansion device; (2) the efficacy of this novel balloon in expanding the ureter to the desired volume while simultaneously providing adequate drainage of the renal unit; (3) a safe and reliable time line schedule and regimen for ureteral balloon expansion; (4) the technical feasibility of performing laparoscopic augmentation ureterocystoplasty using the tissue-expanded ureter; and (5) the biologic nature of the expanded ureteral tissue and its efficacy in providing a urodynamically adequate bladder augmentation in a survival porcine model.

We were able to position the novel balloon satisfactorily through a 20F percutaneous renal tract in all five animals. Important technical maneuvers to facilitate smooth insertion and positioning include dilating the entire ureter to 20F over a Superstiff guidewire and liberal lubrication of the shaft of the balloon catheter. The catheter itself functioned satisfactorily, as judged by balloon integrity and function, as well as proximal urinary drainage in all five animals. Considering the extreme logistical difficulty in maintaining external tubes in active, large animals for a 3- to 4-week period, this finding attests to the reliability of the device. There were no incidents of valve leakage or balloon rupture in our study.

All five animals underwent satisfactory ureteral expansion. We selected an arbitrary inflation schedule, starting at 0.5 mL/day on day 1 and increasing to approximately 20 mL/day by the last day of inflation. The daily amount instilled was increased slowly in the initial 2 weeks of inflation and then more rapidly in the final 2 weeks. This approach was based on the hypothesis that the normal, unexpanded ureter may be more sensitive to rupture early in the expansion process. However, as the expansion proceeds, the expanding ureter becomes thick.

FIG. 8. Autopsy photographs. (A) Augmented bladder and both renal units. Healed suture line between expanded ureteral patch (u) and native bladder (b) is seen (arrows). Right lower ureter underwent expansion (volume 173.5 mL) and subsequent augmentation ureterocystoplasty (bladder capacity 530 mL). Right kidney had grade 5 reflux but no obstruction. (B) Interior of augmented bladder shows clear demarcation (arrows) between expanded ureter (u) and native bladder (b). Notice complete epithelialization of expanded ureteral patch.

FIG. 9. Histologic appearance of expanded ureter harvested at autopsy reveals smooth-muscle hypertrophy and hyperplasia. There is complete regeneration of ureteral transitional epithelium. Difference in thickness of smooth-muscle layer between expanded and normal-caliber ureter is obvious on histologic examination under similar magnification.
and vascular, thereby allowing more rapid expansion. We achieved a mean ureteral expansion of 177 mL over a mean of 25 days. There were no complications during the ureteral expansion process. Additionally, all the awake, unrestrained animals tolerated the daily serial expansion without any apparent pain or discomfort even without any analgesia or anesthesia.

Laparoscopic ureterocystoplasty was technically successful in all five animals. The expanded ureteral segment appeared thick and highly vascular, with variable periureteral adhesions. The mucosa, being more sensitive to pressure, revealed patchy areas of denudation, which had, however, regenerated completely, as evidenced by cystoscopy and histologic examination performed after the augmentation ureterocystoplasty. An important technical caveat during augmentation ureterocystoplasty is to minimize mobilization of the tissue-expanded segment, thereby preserving most of its laterally based blood supply.

A concern about a tissue-expanded ureter is whether it may contract over time. Urodynamically, all five augmented bladders revealed normal capacity and compliance over a follow-up period ranging from 15 days to 3 months. The mean capacity of the augmented bladders at euthanasia was 574 mL. Histologic study of the expanded ureter, performed both at augmentation ureterocystoplasty and at euthanasia, revealed smooth-muscle hypertrophy and hyperplasia. Additionally, transmission electron microscopy confirmed intracellular changes consistent with muscle hypertrophy and hyperplasia. This suggests that the thick, vascularized expanded ureter results from addition of new tissue with a significant smooth-muscle component. This provides a cellular basis for the durability of ureteral tissue expansion. Preliminary assessment of growth factor expression in the expanded ureteral tissue revealed a twofold to threefold increase in TGF-\(\beta_2\), which suggests a molecular basis for ureteral tissue expansion.

Postoperative complications occurred in two animals. One animal, whose ureter was unstented, developed lower-ureteral stenosis, hydronephrosis, and poor ipsilateral renal function, and the other animal had pyelonephritis with urosepsis. At autopsy, the animal with lower-ureteral obstruction revealed flimsy adhesion formation at the junction of the expanded ureter with the proximal normal-caliber ureter. There was no transmural fibrosis on histologic examination of the stenotic area. This obstruction probably represents cross-healing of the opposite ureteral walls following mucosal denudation during the expansion process and can potentially be avoided by stenting at the time of augmentation ureterocystoplasty until reepithelialization is complete.

The clinical implications of this study are obvious. The availability of a urothelium-lined, muscle-backed, autogenous vascularized tissue material for purposes of augmentation, and possibly replacement, of the urinary bladder would indeed be a major advance. Potentially, such a bladder substitute could have mucosal, myogenic, and neurogenic attributes that mirror those of a functionally intact urinary bladder. At the same time, the integrity of the upper tracts must be assured. Considerable additional work remains to be done to realize this hitherto-elusive goal.

**CONCLUSIONS**

Our survival porcine study demonstrates that progressive, incremental ureteral tissue overexpansion can be carried out safely and reliably with a percutaneously placed expansion balloon. This ureteral expansion is well tolerated and can be performed over a 3- to 4-week period to create a sizeable reservoir for bladder augmentation. The expanded ureter is thick and vascular and reveals histologic and electron microscopic features of durable ureteral smooth-muscle hypertrophy and hyperplasia. This expanded tissue can be used laparoscopically to augment the bladder. Such augmented bladders possess good

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<tr>
<th>Specimen</th>
<th>VEGF (pg/mL)</th>
<th>TGF-(\beta_2) (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Control 2</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Treatment 1</td>
<td>2.5</td>
<td>48</td>
</tr>
<tr>
<td>Treatment 2</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td>Treatment 3</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Treatment 4</td>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td>Treatment 5</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td>Treatment 6</td>
<td>0</td>
<td>49</td>
</tr>
<tr>
<td>Treatment 7</td>
<td>44</td>
<td>38</td>
</tr>
</tbody>
</table>

*Growth factor expression was assayed in seven ureteral tissue specimens obtained from five animals at augmentation ureterocystoplasty. All tissue specimens were snap-frozen in liquid nitrogen and processed simultaneously later. Whole-cell protein extracts were obtained by homogenization and centrifugation of tissue specimens in buffered saline with proteinase inhibitors. The ELISAs was performed according to the manufacturer’s instructions (R&D Systems, Minneapolis, MN), and results were normalized to standard samples.

*Control 1 and Control 2 are biopsies of normal porcine ureter to establish baseline values. Treatment 1 through 7 are biopsies from tissue-expanded ureter.
urodynamic properties over a 3-month follow-up period. This approach has the potential to provide native, urothelium-lined tissue for augmentation or replacement of the urinary bladder.

REFERENCES


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