

RESEARCH ARTICLE | *Imaging Techniques in Renal (Patho)Physiology Research*

Novel contrast mixture improves bladder wall contrast for visualizing bladder injury

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Tyagi P, Janicki JJ, Hitchens TK, Foley LM, Kashyap M, Yoshimura N, Kaufman J. Novel contrast mixture improves bladder wall contrast for visualizing bladder injury. *Am J Physiol Renal Physiol* 313: F155–F162, 2017. First published March 29, 2017; doi:10.1152/ajprenal.00609.2016.—Here, we tested whether combined contrast-enhanced magnetic resonance imaging (CCE-MRI), using a mixture of gadolinium- and iron oxide-based contrast agents, can segment the bladder wall from the bladder lumen. CCE-MRI relies on the differences in particle size and contrast mechanisms of two agents for improved image contrast. Under isoflurane anesthesia, T1-weighted imaging of adult female Sprague-Dawley rat bladder was performed using standard turbo spin echo sequences at 7 Tesla, before and after transurethral instillation of 0.3 ml of single-contrast MRI or CCE-MRI composed of 0.4–64 mM of gadolinium chelate (Gd-DTPA/Gadavist) and 5 mM ferumoxytol. Bladder wall contrast was assessed in the control group exposed to saline and in the bladder injury group exposed to 0.5 ml of protamine sulfate (10 mg/ml) for 30 min. CCE-MRI following instillation of 0.4–4 mM Gd-DTPA and 5 mM ferumoxytol mixture achieved segmentation between the bladder lumen and bladder wall. Hyperintensity in the bladder wall combined with hypointensity in the lumen is consistent with the increased diffusion of the dissolved Gd-DTPA and simultaneous localization of the larger nanoparticles of ferumoxytol in the lumen. The normalized hyperintense signal in the bladder wall increased from 0.46 ± 0.07 in control group to 0.73 ± 0.14 in the protamine sulfate-exposed group ($P < 0.0001$). CCE-MRI following instillation of contrast mixture identifies bladder wall changes likely associated with bladder injury with improved image contrast.

gadolinium; ferumoxytol; T1; protamine; combined contrast-enhanced magnetic resonance imaging

MAGNETIC RESONANCE IMAGING (MRI) is one of the best available imaging modalities in urology, since it allows high-contrast images in oblique orientation without the use of ionizing radiation (15). Generally, the bladder wall is seen isointense with urine on T1-weighted images and as a thin hypointense feature distinct from the hyperintense signal of urine on T2-weighted images (11). Therefore, T1-weighted images for staging cancerous growth in the bladder are obtained following injection of gadolinium (Gd)-based contrast agents (GBCA) (17).

Several attempts have been made to explore the intravesical administration of gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA, Magnevist) for contrast-enhanced MRI (CE-MRI) in bladder cancer (18), vesicoureteral reflux (10), and interstitial cystitis (IC) (20). Towner et al. reported increased permeability of Gd-DTPA in the rat bladder following protamine exposure (19). Recently, Towner et al. instilled Gd-DTPA in the bladder of IC patients to demonstrate increased bladder permeability in IC patients relative to healthy controls (20). Intravesical Gd-DTPA was also used to demonstrate the increased permeability of rat bladder following transient exposure to low-energy shock waves (4).

T1-weighted CE-MRI of bladder relies on the differential presence of Gd-DTPA in the lumen following instillation or in the blood volume perfusing the bladder following intravenous injection (17, 19). Intravesical administration of Gd-DTPA was not able to make any value addition over standard intravenous route in the visualization of cancerous growth in bladder wall (18). T2-weighted CE-MRI achieves increased contrast of the bladder wall by shortening the T2 in bladder lumen following instillation of superparamagnetic iron oxide (SPIO) nanoparticles (2). Therefore, past attempts have been unable to achieve sufficient image contrast between bladder wall and lumen following individual instillation of either Gd-DTPA (18) or SPIO nanoparticles (2).

Hence, here we investigate the potential of combined contrast-enhanced magnetic resonance imaging (CCE-MRI) following instillation of GBGA mixed with ferumoxytol (SPIO) (14) in rat bladder before and after protamine sulfate exposure. We hypothesize that different particle size and contrast mechanisms of the two agents on the turbo spin-echo sequences would provide improved image contrast of the bladder wall.

METHODS

Animals

In vivo CCE-MRI experiments. Female Sprague-Dawley rats weighing 250–300 g were procured from Envigo for experimental protocol, approved by the Animal Care and Use Committee (Institutional Animal Care and Use Committee) of the University of Pittsburgh. Animals were anesthetized with isoflurane (1.5–3.0%) for MRI experiments. Bladder injury was induced by 30 min exposure of 500 μ l protamine sulfate (PS, 10 mg/ml, buffered; Fresenius Kabi, Lake Zurich, IL) via a 24-gauge Angiocath intravenous catheter (Becton-Dickinson Infusion Therapy Systems, Sandy, UT) inserted in the urethra. At the end of 30 min, PS was removed by manual compres-

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sion of the lower abdomen followed by two 500- μ l saline washes before instillation of contrast agent. Combined-contrast mixture composed of 5 mM ferumoxytol mixed with 0.4–64 mM of Gd-DTPA (Gado-DTPA; BioPAL, Worcester, MA) or its nonionic substitute Gadobutrol (Gadavist; Bayer) in 300 μ l of normal saline was instilled before PS exposure and immediately following PS exposure.

Instruments. A 7-Tesla 30-cm-bore Bruker ClinScan system equipped with an 86-mm volume transmit coil and a four-channel array receive coil was used for imaging. Animal temperature was maintained at 37°C, and respiration was monitored (SA Instruments, Stony Brook, NY) during the scan. MRI images were acquired using a Turbo Spin-Echo sequence, with a repetition time (TR) of 500–7,000 ms, echo time (TE) of 10–36 ms, 2-mm slice thickness, a 256 \times 256 matrix and a 6 \times 6 cm² field of view (FOV), and two signal averages. Higher-resolution images were acquired using a 2 \times 2 mouse cardiac array coil via a generalized autocalibrating partial parallel acquisition (GRAPPA) scheme (2 \times) with the same parameters as above except for a 512 \times 504 matrix, a 2.4 \times 2.5 cm² FOV, and a 0.7-mm slice thickness (10). All images were acquired using motion and fat suppression.

Ex vivo T1 maps. Ex vivo T1 maps were constructed to arrive at optimal CCE-MRI parameters that were sensitive to the accumulation of Gd concentration in the bladder wall during subsequent in vivo experiments following PS exposure. Full T1 maps could not be obtained in the in vivo state because of significant urine production over the time required to acquire the T1 maps. Under anesthesia, either saline or PS was instilled in the rat bladder for 30 min, which was then drained and washed with saline. Subsequently, animal was euthanized, combined-contrast agent mixture (4 mM Gadavist + 5 mM ferumoxytol) was instilled, and the bladder neck was tied off with suture before excision. Excised bladder was placed in a tube containing 30 mg/ml gelatin solution (in water) at ambient temperature. The gelation of the solution was induced by incubation in a cold water bath (4°C) for ~15 min before imaging. The bladder encased in the gel was imaged in a series of spin-echo experiments with TR of 100, 250, 500, 750, 1,000, 2,500, 5,000, and 10,000 ms. Signal intensities were sampled from the bladder wall at each TR, and a nonlinear least-squares curve fit was constructed on the T1 relaxation function $SI = A(1 - e^{-TR/T1}) + c$ to obtain an estimate of the T1 values for bladder wall with and without PS exposure, where SI is the observed signal intensities, and T1, A, and c are the parameters that optimized to perform the fit. From the resulting curves, TR values of 500–1,000 ms were selected for comparing the in vivo imaging of two groups.

Histology

The bladder was excised from the animals euthanized at the end of imaging, which was then filled with 10% formalin for gross morphological evaluation. Subsequently, the bladder was cryoembedded, sectioned, and stained with hematoxylin and eosin (Fisher Scientific).

Data Analysis and Statistics

MRI signal intensity of the bladder wall assessed on T1-weighted spin-echo images was normalized to the corresponding intensity of the thigh muscle of the same animal. Significance at $P < 0.05$ was analyzed using unpaired Student's *t*-test with GraphPad Prism Software (La Jolla, CA). Data are shown as means \pm SD.

RESULTS

Optimization of Gd-DTPA Concentration

We first assessed the effect of altering the TE on different phantom concentrations of Gd-DTPA in a plastic tube (Fig. 1) at fixed TR of 650 ms. Four tubes filled only with 4, 16, 64, and 256 mM Gd-DTPA (without the inclusion of ferumoxytol) were placed on the abdomen of control rats and shown as insets in Fig. 1, A and B. Signal from higher concentrations of Gd-DTPA (256 and 64 mM) was undetectable at the longer TE of 36 ms. Except for 256 mM, the signal from 4, 16, and 64 mM Gd-DTPA was visible at TE of 10 ms, with the intensity being lowest for 64 mM, suggesting that signal intensity drops at higher Gd-DTPA concentration possibly because of a magnetic susceptibility effect (16). Increasing the TE from 10 to 36 ms emphasizes this susceptibility effect (Fig. 1, A and B).

In Vivo Optimization of Gd-DTPA Concentration for CCE-MRI

The image contrast of the bladder wall before instillation of contrast agent was higher at a TE of 36 ms compared with imaging at 10 ms (Fig. 1, A and B). High transverse relaxivity of ferumoxytol (5 mM) present in the combined-contrast mixture can further improve the contrast observed between bladder wall and lumen at the TE of 36 ms (Fig. 2, E and F). We assessed the improvement in image contrast of the bladder wall

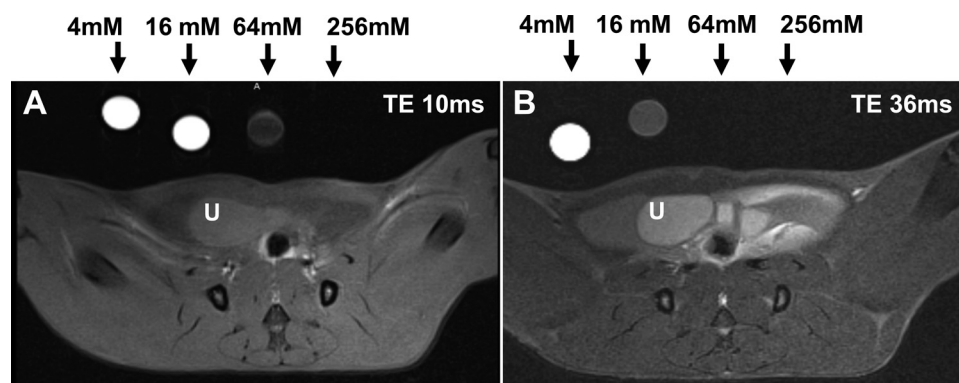


Fig. 1. In vitro optimization of gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA) concentration for contrast-enhanced magnetic resonance imaging (CE-MRI). Four tubes filled with ascending concentration of only Gd-DTPA from left to right of 4, 16, 64, and 256 mM placed on the abdomen of two different rats for T1-weighted imaging at the repetition time (TR)/echo time (TE) of 650/10 and 650/36 ms in A and B, respectively. Images of tubes are seen as insets in axial images of urine-filled rat bladder taken simultaneously. The 4th tube on the right filled with 256 mM is undetectable at TE of 10 and 36 ms. The 3rd tube filled with 64 mM Gd-DTPA is only visible at the lower TE of 10 ms (A) and undetectable at the higher TE of 36 ms (B). In contrast, the tube with the lowest concentration of Gd-DTPA (4 mM) shows bright signal at TE of 10 and 36 ms. The increase in TE also increased the contrast between bladder wall and lumen containing urine (U) in B relative to A.

afforded by the inclusion of GBCA in the contrast mixture, Gd, in the dose range 0.4–32 μmol Gd/kg. Rat bladder was instilled with a higher concentration (64 mM) (Fig. 2, *A* and *B*) and a lower concentration (4 mM) of Gd-DTPA (Fig. 2, *C–F*), while keeping the ferumoxytol (5 mM) constant in the combined-contrast mixture. We noted that Gd-DTPA (64 mM) produced a hyperintense signal on the serosal side of the bladder (Fig. 2, *A* and *B*) that was eliminated at the lower concentration of Gd-DTPA (4 mM) (Fig. 2, *C–F*).

Axial and corresponding sagittal slices (Fig. 2, *A* and *B*) verified that the origin of hyperintensity (artifact) is indeed outside of the bladder wall (Fig. 2, *C–F*). Hyperintensity is primarily seen in the frequency encode direction (Fig. 2, *A* and *B*), suggesting high concentration of paramagnetic metal (Gd) in the bladder lumen could cause a chemical shift in the water resonance frequency. Phantom bladders, which consisted of single bubbles of plastic bubble wrap, were filled with GD-DTPA or a GD-DTPA-ferumoxytol mixture, sealed with adhesive, and set in gelatin. These were used to confirm that the observed artifact (Fig. 2, *A* and *B*) arises from the localization of Gd-DTPA in high concentration. We found that the artifact always occurs in the direction of the magnetic field and that it is sensitive to changes in acquisition bandwidth (data not shown). Overall, image contrast of bladder in CCE-MRI is optimal at TR/TE of 650/36 ms and at the Gd-DTPA concentration ≤ 4 mM. The effect of the longer TE was similar to the

instillation of an eightfold higher concentration of Gd-DTPA (Fig. 2, *E* and *F*).

Comparative Advantage of CCE-MRI Over CE-MRI

Higher-resolution single-slice images of a control rat bladder (Fig. 3, *A–D*) were acquired longitudinally at baseline (with urine present in the lumen) and after instillation of CE-MRI or CCE-MRI. Images were acquired with use of GRAPPA at TR/TE of 500/15 ms, where CE-MRI following instillation of either 5 mM ferumoxytol or 4 mM Gadavist (nonionic substitute for Gd-DTPA) could not easily distinguish the lumen from the bladder wall (Fig. 3, *B* and *C*). Solitary presence of ferumoxytol (5 mM) in lumen made the bladder uniformly dark in T1-weighted images (Fig. 3*B*), whereas the sole presence of Gadavist (4 mM) made it uniformly bright (Fig. 3*C*). However, CCE-MRI after instillation of the combined-contrast mixture increased the contrast with the thin strip of hyperintense signal in bladder wall easily distinguishable from the hypointense signal in the lumen (Fig. 3*D*). The contrast seen with CCE-MRI at TR of 500 ms in Fig. 3*D* becomes more pronounced when multiple MRI image slices are acquired at the higher TR of 3,000 ms and TE of 15 ms without using GRAPPA (Fig. 3*E*). Instead of a single-image slice acquired by the MRI for the image shown in Fig. 3*D*, the image in Fig. 3*E* is one of five

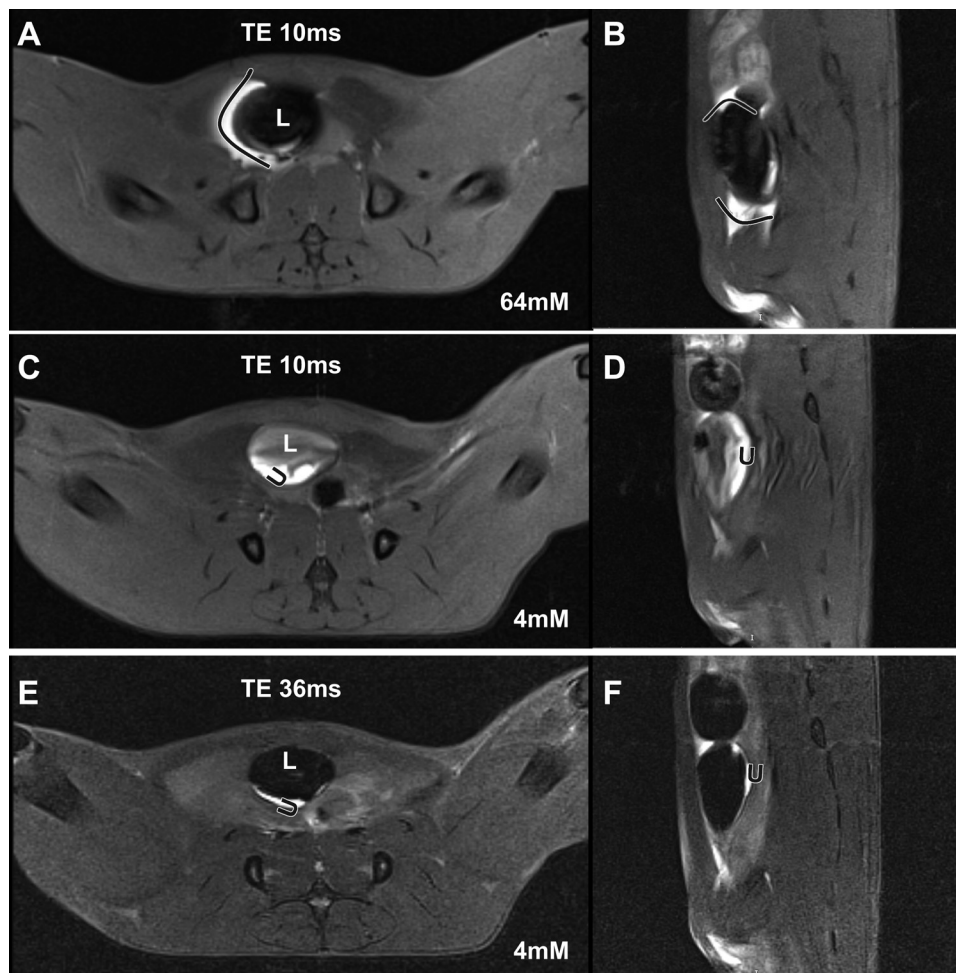


Fig. 2. In vivo optimization of Gd-DTPA concentration for combined contrast-enhanced magnetic resonance imaging (CCE-MRI). *A–D* (TR/TE of 650/10 ms): axial and sagittal T1-weighted images of PS-exposed bladder instilled with 0.3 ml of contrast mixture composed of 5 mM ferumoxytol mixed with either 64 (*A* and *B*) or 4 (*C* and *D*) mM Gd-DTPA (slice thickness 2 mm). The hyperintensity artifact (indicated by dotted red curve) on the serosal side of the bladder seen in *A* and *B* occurs with the use of higher gadolinium concentrations (64 mM) likely because of chemical shift. The artifact disappears at the lower concentration of Gd-DTPA (4 mM). Corresponding axial and sagittal images of rat bladder shown in *C* and *D* following acquisition at TR/TE of 650/36 ms are shown in *E* and *F*. The hypointensity in the bladder lumen seen with 64 mM Gd-DTPA at TE of 10 ms can also be achieved at an 8-fold lower concentration of 4 mM by raising the TE to 36 ms from 10 ms. Red U indicates the presence of urine below contrast mixture (L) in bladder lumen.

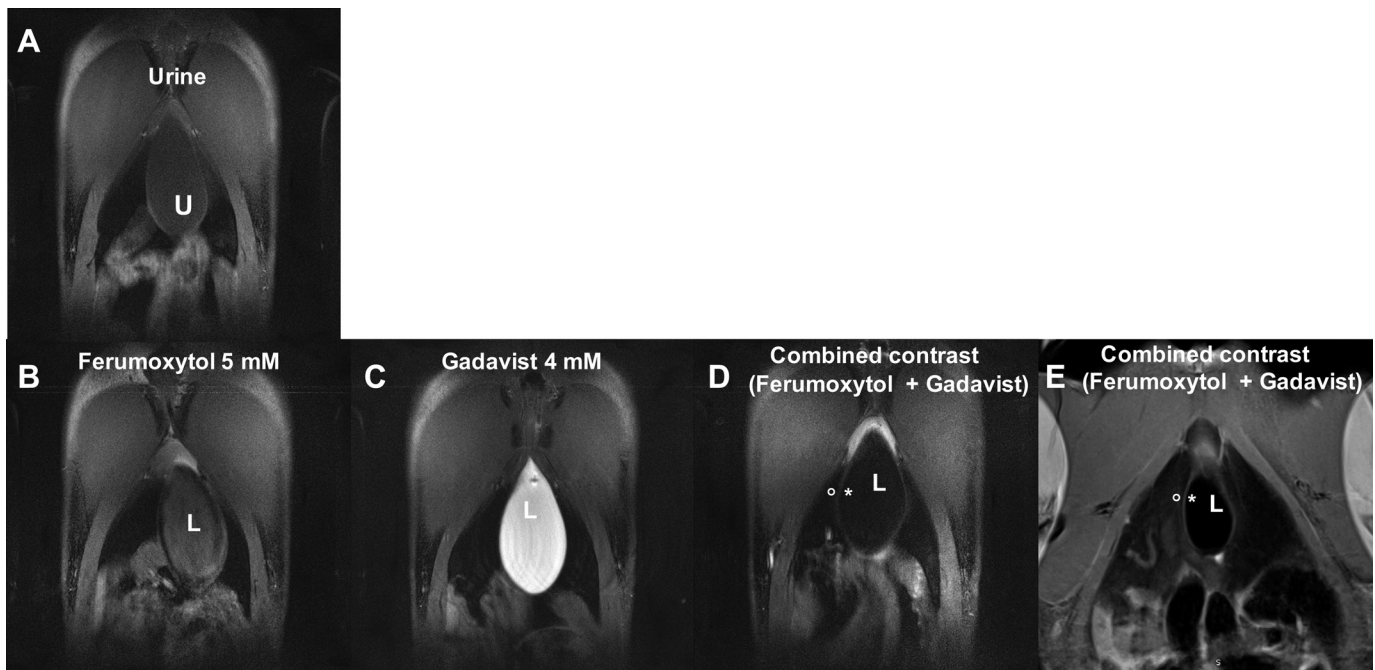


Fig. 3. Comparison of CE-MRI and CCE-MRI at identical parameters of TR/TE of 500/15 ms in a single coronal slice of control rat bladder. *A*: baseline image with the presence of urine. *B*: CE-MRI of bladder taken only after instillation of 0.3 ml of ferumoxytol (5 mM). *C*: CE-MRI of bladder taken only after instillation of 0.3 ml of Gadavist (4 mM). *D*: CCE-MRI of bladder with 0.3 ml of contrast mixture of ferumoxytol (5 mM) mixed with Gadavist (4 mM). *E*: similar to *D* with regard to instilled contrast mixture; only differs in imaging parameters. CCE-MRI in *E* was performed at 6 times higher TR of 3 s for acquiring multiple image slices instead of a single image slice with (2-factor) generalized autocalibrating partial parallel acquisition acceleration shown in *A–D*. *E* represents 1 of the 5 image slices acquired of bladder (each slice thickness 2 mm). In contrast to CE-MRI, CCE-MRI is able to successfully resolve the luminal (*) and serosal (°) boundaries of the bladder wall. The presence of urine in bladder lumen is indicated by U in *A*, and the presence of contrast mixture in the bladder lumen is indicated by L in *B–E*.

image slices acquired of the rat bladder, where each image slice represents a bladder section of 2 mm thickness.

CCE-MRI Following PS Exposure

A combined-contrast mixture composed of 5 mM ferumoxytol + 4 mM of Gd-DTPA (or substitute) was instilled in animals previously exposed to either saline or 0.5 ml of PS (10

mg/ml) for 30 min. PS exposure increased the signal intensity of bladder wall, presumably because of the increased permeability for Gd-DTPA present in lumen. Signal intensity (Fig. 4, *A–C*) was compared at TR of 1,000 ms because of the observed differences in the signal-to-noise ratio of two groups at that TR. Lower TR values, especially 100 and 250 ms, had a lower signal-to-noise ratio and, in some cases, made segmentation of

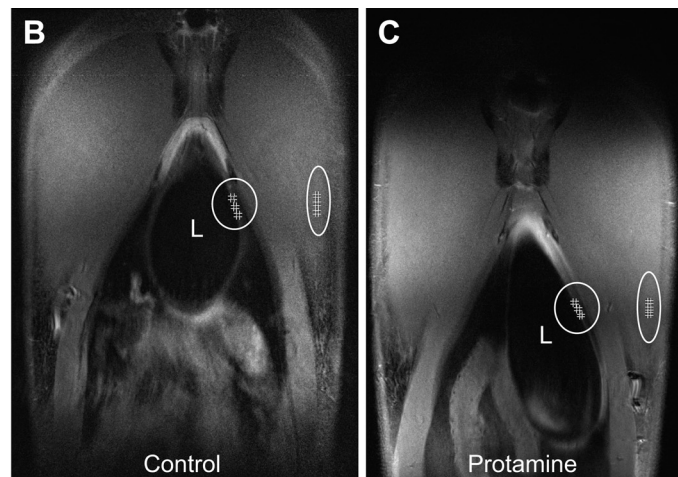
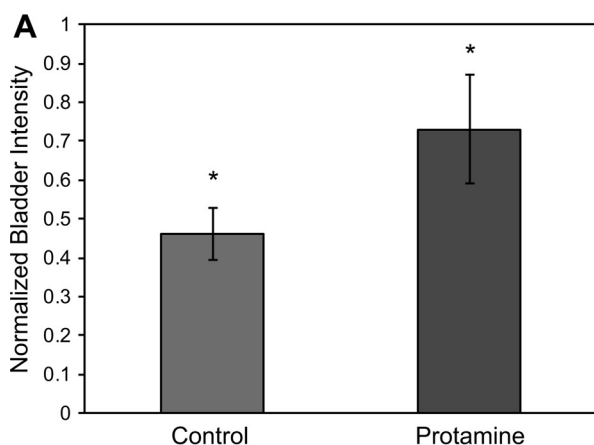


Fig. 4. Quantitative signal assessment in bladder wall. *A*: normalized signal intensities measured with CCE-MRI in control ($n = 3$) and protamine sulfate (PS)-exposed ($n = 5$) animals at TR/TE of 1,000/15. *B* and *C*: representative images from each group. The signal intensity in three regions of bladder tissue (circles) was normalized by thigh muscle intensity (ovals) so that comparisons between different images of two groups are valid. Significant increase in signal intensity in the PS group was assessed by Student's *t*-test with unpaired (* $P < 0.0001$). The presence of contrast mixture in the bladder lumen is indicated by L in *B* and *C*.

bladder pixels difficult. The control and PS groups had an average T1 of 2.4 and 1.6 s of the bladder wall, respectively. The reduction in T1 of the PS group was expected because diffusion of Gd chelates in the bladder wall from the lumen, which then interacts with the spin of water protons to reduce the tissue T1. The normalized intensity of the bladder wall in the control group of 0.46 ± 0.07 was significantly increased to 0.73 ± 0.14 in the PS group (unpaired Student's *t*-test; 2-tailed, $P = 0.00002$).

Gross Morphology and Histology

Bladders of control and PS-exposed groups were harvested after CCE-MRI for gross morphology (Fig. 5, A and B) and histology (Fig. 5, C and D). Gross morphology indicated increased dilation of the blood vessels because of inflammatory changes induced by acute exposure to PS (12, 13). Histology of the PS-exposed bladder revealed vascular congestion, edema, and infiltration of inflammatory cells (Fig. 5, D and F). In contrast, only edema was noted in the control group (Fig. 5, C and E) presumably because of the multiple catheterizations needed for the MRI protocol.

Temporal Imaging

Four different coronal slices of the rat bladder previously exposed to PS were acquired immediately, 30 min, and 60 min after instillation of a combined-contrast mixture (5 mM ferumoxytol + 0.4 mM Gd-DTPA). Except for the slice shown in Fig. 6A, a thin strip of high-intensity signal grows progressively in successive slices to demonstrate the progressive accumulation of urine in the bladder after instillation. The bottommost slice at each time point, shown in Fig. 6, D, H, and L, had the highest amount urine signal (indicated by U), indicating that signal of fresh urine coming from the ureters is enhanced. The inserted catheter filled with combined contrast is visible as dark black tubing (parallel to the red line) in corresponding slices at each time point in Fig. 6, C, G, and K.

DISCUSSION

We presented here a novel CCE-MRI technique for reliably segmenting the mucosal and the serosal side of the rat bladder wall. Overall, our findings support the hypothesis that the diffusion of Gd chelates away from the combined-contrast mixture localized in the lumen allows the bladder wall to be

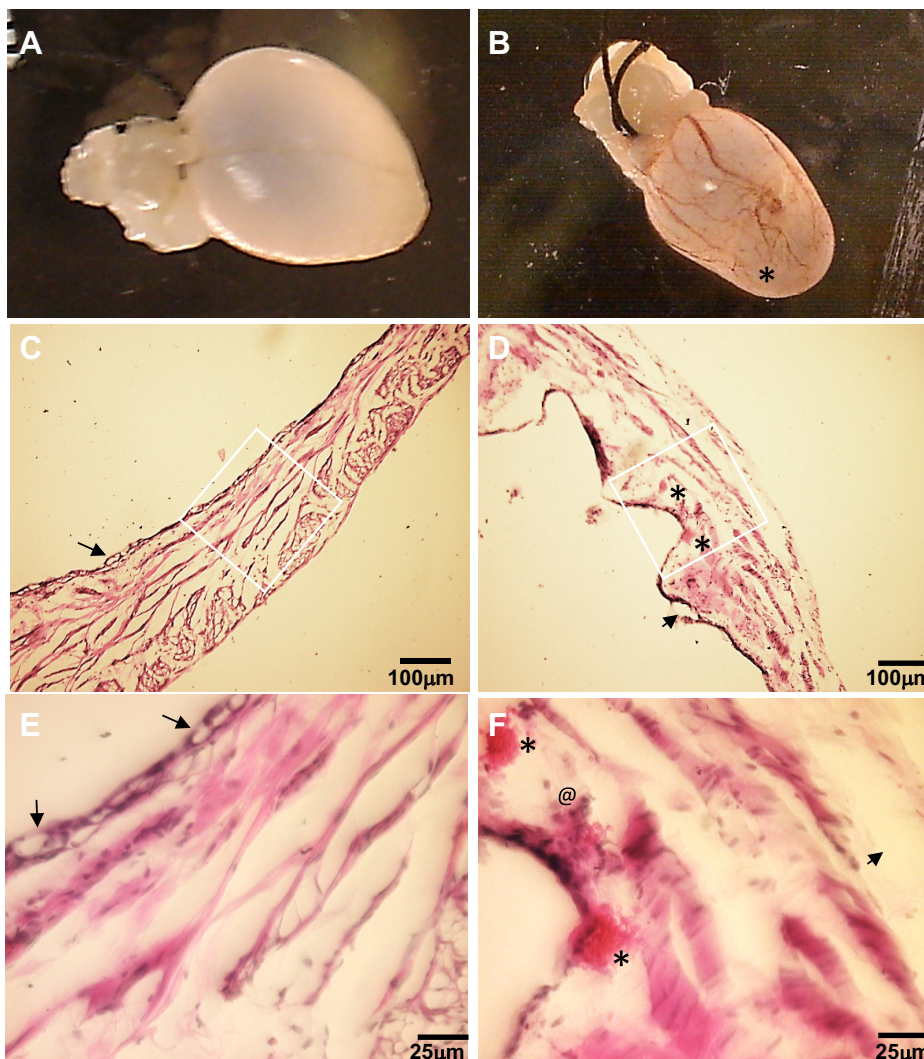


Fig. 5. A–D: morphology and histology of harvested bladder. Gross morphology of the control group indicated only mild mucosal edema (A), whereas acute PS exposure induced inflammatory changes as shown by dilated blood vessels (Telangiectasia; * in B). Histological changes induced by PS exposure (D) are indicated by severe edema (arrow) with instances of submucosal hemorrhage and Telangiectasia (*) and infiltration of inflammatory cells (@). Mild mucosal edema is also noticeable in the control group (C). Regions outlined in the white box in C and D are magnified in E and F, respectively.

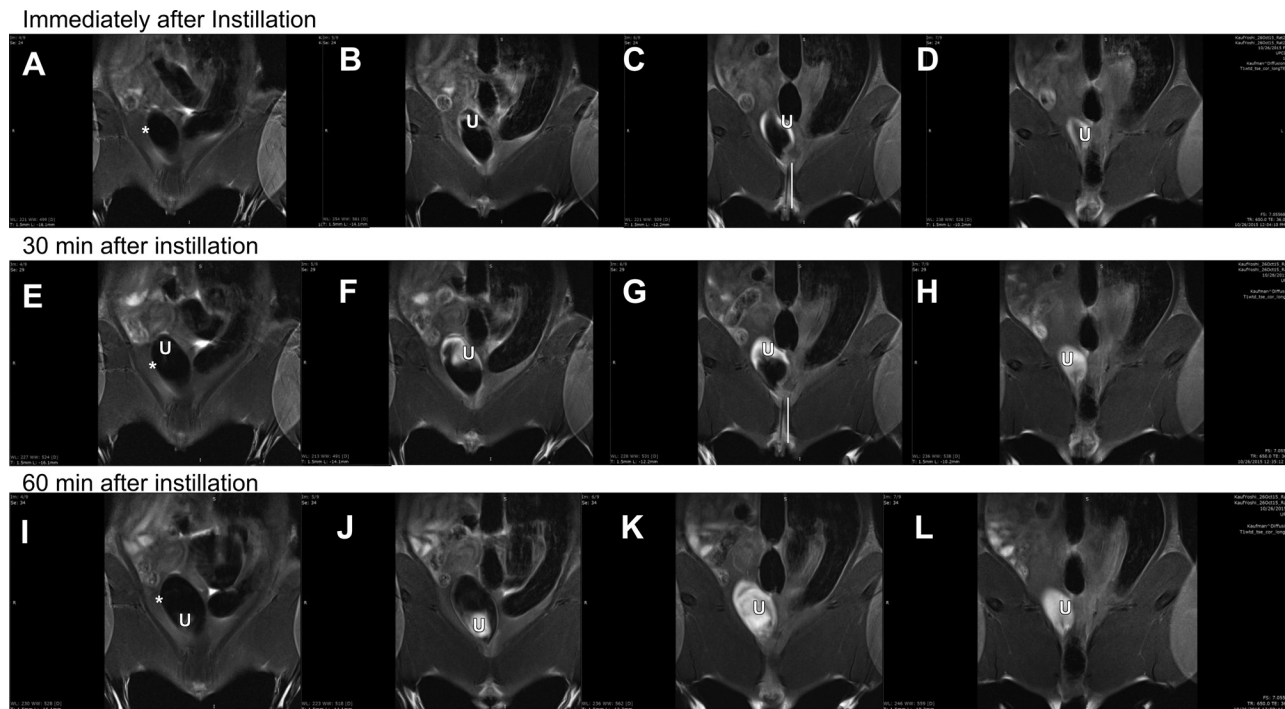


Fig. 6. Longitudinal CCE-MRI. Successive 2-mm coronal T1-weighted slices at TR/TE of 650/36 ms for each time point are arranged *left to right* in longitudinal CCE-MRI performed following instillation of 5 mM ferumoxytol mixed with 0.4 mM Gd-DTPA in 0.3 ml. *A–D*: successive slices taken immediately after instillation. Notice that layer of intense signal from urine (U) is visible in all panels except for *A*. The bladder wall is visible (*) in *A*, *E*, and *I*. The slice at the bottom of bladder for each time point is shown in *D*, *H*, and *L*: where urine signal progressively increases because of diffusion of Gd-DTPA away from the combined-contrast mixture (seen as intense dark signal in the preceding slices and most prominently in the top most slice of bladder shown in *A*, *E*, and *I*). Two slices at the 60-min time point are completely filled with urine (area of intense signal) as seen in *K* and *L* compared with only one slice (*D* and *H*) for other time points to confirm the time-dependent diffusion of contrast agents into urine. The area of intense signal progressively increases in slices shown in *B*, *C*, *F*, *G*, and *J*. The catheter inserted in the urethra filled with contrast mixture is distinctly visible in slices *C* and *G*, but increased quantity of urine occludes the catheter in *K* acquired 60 min after instillation. Catheter is visible as the black line parallel to the drawn red line.

visualized with a bright signal due to T1 relaxation enhancement of the water molecules in the bladder wall, while ferumoxytol simultaneously quenches the signal from the bladder lumen in turbo spin-echo sequences. The large molecular size of ferumoxytol (14) is responsible for its retention in the bladder lumen and exhibition of image hypointensity from the rapid SPIO-dominated T2 relaxation whereas the partitioning of Gd in the bladder wall causes T1-weighted image hyperintensity.

CCE-MRI was demonstrated to be superior to CE-MRI in visually segmenting the bladder wall from the lumen and the surrounding tissue. Intense T1 signal throughout the bladder following sole instillation of Gd chelate for CE-MRI corroborates previous preclinical and clinical findings (4, 18, 19), where visual separation of bladder wall from lumen and its demarcation from perivesicular fat is difficult, even when applying fat suppression methods. CCE-MRI demonstrated that the T1 value of 2.4 s measured in the bladder wall of the control group decreased significantly to 1.6 s after PS exposure. Signal intensity of the bladder wall between the TR ranging from 500 to 1,000 ms was sensitive to the diffusion of Gd, and therefore comparison at the TR of 1,000 ms was chosen to detect the differences between the control and PS-exposed rat bladder.

The optimal intravesical concentration range for the Gd-DTPA in CCE-MRI is in agreement with the concentration range used in human study (10). Decreased signal intensity at

a higher concentration of Gd-DTPA in patients (3) is caused by the dominance of Gd- and DTPA-mediated T2 relaxation over T1 relaxation (6). In our experimental protocol, MRI were acquired in different orientations and echo times to assess the authenticity of hyperintense artifact seen on the serosal side of the bladder with a high concentration of Gd-DTPA.

We found that intensity of the bright artifact on the serosal side of the bladder was primarily in the direction of the magnetic field and was sensitive to the concentration of Gd-DTPA and receiver frequency bandwidth. The serosal side of the rat bladder is adjacent to perivesical fat and air (which is partly diamagnetic) that is typically aspirated before intraperitoneal injection (21). Therefore, it is presumed that high localized concentration of paramagnetic Gd in the lumen facilitates the differences in resonance frequency of fat/water to be mistaken for the differences in spatial position of fat signal in the frequency-encoding direction at the interface of the perivesical fat/air of bladder. The instillation of Gd-DTPA within the concentration range of 0.4–4 mM reduces the concern of chemical shift and magnetic susceptibility artifact (5) in the findings described here.

Moreover, PS exposure in the experimental conditions used here is expected to increase the permeability of the mucosal side of the bladder and not of the serosal side. Hence, bright artifact on the serosal side of the bladder cannot be from the efflux of Gd-DTPA outside of the bladder wall.

From previous studies it is known that ferumoxytol causes hypointensity on T2-weighted images at all concentrations but may also show hyperintense signal on T1-weighted images in areas of low concentration (2, 9, 13). Therefore, we used relatively high concentration of ferumoxytol (5 mM Fe content) in our CCE-MRI to ensure optimal contrast between lumen and the bladder wall. Normally, urine has high T2 and low T1 signal intensity, but blood components or inflammatory cells can cause appearance of a hyperintense signal in urine. Therefore, diffusion of both Gd and ferumoxytol from the combined-contrast agent mixture could be responsible for the increased T1 signal of urine (2, 9, 13), which could have potential application in diagnosing urological disorders, including refluxing of urine in ureter in the vesicoureteral reflux (10).

CCE-MRI findings were consistent with the gross morphological and histological changes in the bladder following PS exposure. We found that the image contrast of the bladder wall improved regardless of the charge carried by Gd chelate in the concentration range 0.4–20 mM although it is likely that the anionic nature of Gd-DTPA (7) may be suboptimal for assessing the influx of the intact chelate in the bladder wall, which is known to have sulfated sugar residues on the luminal surface (8). Both the T1 and T2 relaxing agents used here are approved by the US Food and Drug Administration, and their clinical safety following intravesical administration is known (2, 10, 15, 18, 22).

CCE-MRI has potential in distinguishing morphological abnormalities such as diffuse vs. a focal disruption of bladder wall integrity in patients with cystitis. Improved bladder wall contrast coupled with tonicity measurements of levator ani (1) by MRI can facilitate diagnosis and streamline the treatment of cystitis patients. Because CCE-MRI facilitates dark appearance of the bladder lumen, it can remove the existing deficiencies in the assessment of toxin migration in the bladder using MRI (12).

Conclusions

This study represents an advancement in the field with clinical implications. MRI following instillation of a combined-contrast mixture can enable better visualization of cystitis because of increased permeability of the bladder to Gd chelates.

GRANTS

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DISCLOSURES

Joseph J. Janicki and Jonathan Kaufman are employees of Lipella Pharmaceuticals.

AUTHOR CONTRIBUTIONS

P.T., N.Y., and J.K. conceived and designed research; P.T., J.J.J., T.K.H., L.M.F., M.K., and J.K. performed experiments; P.T. and J.J.J. analyzed data; P.T., J.J.J., and J.K. interpreted results of experiments; P.T., J.J.J., and M.K. prepared figures; P.T. drafted manuscript; P.T., J.J.J., T.K.H., and J.K. edited and revised manuscript; P.T., N.Y., and J.K. approved final version of manuscript.

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