Dendrimer-enhanced MRI as a diagnostic and prognostic biomarker of sepsis-induced acute renal failure in aged mice

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Background. Acute renal failure (ARF) induced by sepsis has a high mortality. In an aged mouse model of sepsis-induced ARF we have previously shown that renal injury occurs before serum creatinine is elevated. Development of a noninvasive biomarker that could diagnose renal dysfunction early in sepsis and monitor the response to therapy would be very valuable.

Methods. We performed magnetic resonance imaging (MRI) with gadolinium-based G4 dendrimer intravenous contrast in a fluid- and antibiotic-treated cecal ligation and puncture (CLP) sepsis model in aged mice. Imaging was also performed in a mouse volume depletion model and in models of ARF induced by ischemia/reperfusion (I/R) and cisplatin.

Results. Twenty hours post-CLP, aged mice had a distinct pattern of renal injury using dendrimer-enhanced MRI. This pattern was different from renal injury induced by either cisplatin or I/R. Prerenal azotemia induced by volume depletion was distinguished from sepsis by dendrimer-enhanced MRI. Dendrimer-enhanced MRI detected renal dysfunction 6 hours post-CLP, a time when serum creatinine was still normal. Ethyl pyruvate reversed the renal dysfunction detected by dendrimer-enhanced MRI at 20 hours, but not at 6 hours post-CLP. The appearance of renal dysfunction on dendrimer-enhanced MRI at 6 hours post-CLP predicted the length of survival.

Conclusion. Dendrimer-enhanced MRI is a novel biomarker that provides information for the early diagnosis, drug responsiveness, and prognosis of sepsis-induced ARF.

Acute renal failure (ARF) is a relatively common life-threatening illness occurring in 5% to 20% of intensive care unit patients [1–3]. Sepsis is a major cause and sepsis-induced ARF has a particularly poor outcome with a mortality of 50% to 80% [4–6]. This is in stark contrast to ARF from other causes, for example, ARF induced by nephrotoxic radiocontrast has a reported mortality as low as 2% [7]. Therefore, treatments to prevent or treat sepsis-induced ARF are highly sought after to alleviate this condition. If therapies are to be effectively tested in human studies then renal impairment needs to be diagnosed early in a septic patient and the cause be differentiated from other insults such as ischemia and nephrotoxins. Development of a noninvasive biomarker which could detect renal injury early, locate the site of injury, and determine the cause would be extremely valuable. For drug development it would be very useful if the biomarker could track successful drug treatment and serve as an intermediate end point. This paper describes the results using one such biomarker: a novel magnetic resonance imaging (MRI) technique.

The renal ischemia/reperfusion (I/R) model is often used as a rodent model of ARF [8]. However, the pattern of renal injury after sepsis is different from that following I/R [9]. A mouse model of sepsis-induced ARF has recently been developed based on the cecal ligation and puncture (CLP) technique to generate polymicrobial sepsis [10]. This model is distinct from typical mouse CLP models in that fluid and antibiotic resuscitation is administered to aged mice. The mice develop multiorgan failure, including ARF, which resembles human sepsis. Histologic changes consist of vacuolization throughout the kidney and no inflammation, quite distinct from ischemic or nephrotoxic models. The lack of striking renal histological changes is similar to the findings at human autopsy of septic patients [11]. The protein biomarker CYR61 is increased in both ischemic- and sepsis-induced ARF and, therefore, cannot distinguish the cause [10, 12]. However, using histology and kidney tissue CYR61, it appears that renal injury occurs early in sepsis; up to 6 hours before serum creatinine is raised. This suggests that in sepsis there is an early “silent” period of ARF before the serum creatinine becomes elevated.
We have previously demonstrated that dynamic high-resolution micro-MRI combined with a novel dendrimer-based macromolecular renal MRI contrast agent (“dendrimer-enhanced MRI”) can be a powerful tool for in vivo observation of renal structure, function, and injury [13, 14]. In this paper we investigate whether this technique can be used as a biomarker for sepsis-induced ARF.

METHODS

Animals

Animal care followed National Institutes of Health (NIH) criteria for the care and use of laboratory animals in research. Young (7 to 8 weeks) female BALB/c nu/nu mice and aged (42 to 44 weeks) male C57BL/6 mice (NIH, Frederick, MD, USA) had free access to water and chow (NIH-07 Rodent Chow), except during volume depletion studies (Zeigler Bros., Gardners, PA, USA), before and after surgery. Aged mice were housed individually.

CLP-induced ARF

Aged C57BL/6 mice were anesthetized using isoflurane inhalation. After laparotomy, a 5–0 silk ligature was placed 1 cm from the cecal tip. The cecum was punctured twice with a 21-gauge needle and gently squeezed to express a 1 mm column of fecal material. In sham-operated animals, the cecum was located, but neither ligated nor punctured. The abdominal incision was closed in two layers with 6–0 nylon sutures. After surgery, 1 mL of prewarmed normal saline was given intraperitoneally and 1.5 mL given subcutaneously. All animals received a broad-spectrum antibiotic (imipenem/cilastatin 14 mg/kg subcutaneously) at 6 hours, and 1.5 mL of 3/4 normal saline was administered at 6 and 18 hours after surgery by subcutaneous injection. At the time of sacrifice, blood was collected by cardiac puncture for measurement of serum creatinine by high-performance liquid chromatography (HPLC) [15] and the kidneys were harvested for histologic evaluation. The 10% formalin-fixed, paraffin-embedded kidney sections were stained with periodic acid-Schiff (PAS) reagent.

For survival studies the size of the needle used for cecal puncture was varied between 21 and 28 g. The animals were monitored twice daily and received 1.5 mL 3/4 normal saline and antibiotic twice daily. Those mice surviving to day 7 were imaged again by dendrimer-enhanced MRI.

Effect of ethyl pyruvate on CLP-induced ARF

Aged C57BL/6 mice received 0.4 mL of Ringer’s lactate (130 mmol/L Na⁺, 4 mmol/L K⁺, 2.7 mmol/L Ca²⁺, 109 mmol/L Cl⁻, and 28 mmol/L lactate) or a similar volume of freshly made Ringer’s ethyl pyruvate where isomolar ethyl pyruvate (Sigma Chemical Co., St. Louis, MO, USA) was substituted for sodium lactate. Doses were injected intraperitoneally at 0 and 6 after CLP surgery.

Volume depletion

Aged C57BL/6 mice were weighed then received two subcutaneous injections of furosemide (40 mg/kg) 3 hours apart. Control mice received two injections of sterile water vehicle. Furosemide-treated mice then were given free access to low sodium diet (Teklad, Madison, WI, USA) (Diet no. 7034) (sodium 0.1%). Control mice had free access to NIH-07 Rodent Chow (Zeigler Bros.) (sodium 0.31%). Twenty-four hours after the first injection, the mice were reweighed, then MRI was performed. After imaging, urine was collected directly from the bladder and blood was collected by cardiac puncture.

Cisplatin-induced nephrotoxicity

Seven-week-old female BALB/c nu/nu mice were injected intraperitoneally with 400 μg of cisplatin (Sigma Chemical Co.) in 400 μL of saline without anesthesia. The mice were studied by micro-MRI 3 days after the cisplatin injection.

I/R-induced ARF

Seven-week-old female BALB/c nu/nu mice were anesthetized with an injection of 100 mg/kg ketamine, 10 mg/kg xylazine, and 1 mg/kg acepromazine intramuscularly. The abdomen was shaved, a midline incision was made, and both renal pedicles were cross-clamped for 40 minutes. Both kidneys were inspected for ischemia after 2 minutes. To help maintain thermoregulation during surgery, the abdomen contents were replaced and the abdomen was temporarily closed with several sutures. The abdomen was reopened 40 minutes after clamping and the clamps were removed. The kidneys were again inspected for restoration of blood flow, and 1 mL of prewarmed normal saline was instilled into the abdominal cavity. The abdomen was closed in two layers, and MRI images were obtained 4 hours later.

Dendrimer-enhanced MRI

The method for synthesis of contrast agent was previously described [13]. Dynamic three-dimensional micro-MRI scans of the kidney in the mice were obtained with injection of 0.03 mmol gadolinium (Gd)/kg of G4D-(1B4M-Gd)₆₄ using a 1.5 Tesla (T) superconductive magnet unit (Signa LX, General Electric Medical System, Milwaukee, WI, USA). All images were obtained using a 1 inch round surface coil (Birdcage type) fixed by an in-house constructed coil holder. The mice were anesthetized with 1.15 mg of sodium pentobarbital (Dain- abot, Tokyo, Japan) and placed at the center of the coils. To avoid artifacts from bowel movement, 2.5 mg of butylscopolamine was added to the anesthetized agent. For the dynamic study, the T1-weighted magnetization
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Fig. 1. The effect of sepsis on dendrimer-enhanced magnetic resonance imaging (MRI) of the kidney. MRI scans 1, 9, and 17 minutes after intravenous injection of G4 dendrimer. (A) Sham-operated mouse 20 hours after surgery, (B) Cecal ligation and puncture (CLP)-operated mouse 20 hours after surgery.

prepared three-dimensional fast-spoiled gradient-echo technique with chemical fat-suppression was used for all mice. The images were acquired at preinjection and 1, 3, 5, 7, 9, 11, 13, 15, and 17 minutes after injection of the contrast agent. After 20 minutes, a full-body image was obtained. The coronal images were reconstructed with 0.8 mm section thickness with 0.4 mm overlap. The field of view was 8 × 4 cm and the size of matrix was 512 × 256. The slice data were analyzed using commercial software (Advantage Windows, General Electric Medical System).

The MRI changes were scored by three criteria: (1) presence of stripes in outer medulla/cortex: 1, clearly present; 2, vague; and 3, none; (2) contrast in pelvis: 1, present and 3 none; and (3) kidney tissue “brightness” compared to renal vein: 1, kidney brighter than vessels; 2, vessels same as kidney; and 3, kidney darker than aorta/renal vessels or blood vessels visible over kidney. The three subscores were added together. Therefore, the score range is from 3 (normal) increasing to 9 with increasing injury. The MRI scans were scored by two masked independent referees and a consensus score determined.

Statistics
Results are expressed as mean ± SEM. Significance was determined by unpaired t test.

RESULTS
Dendrimer-enhanced MRI in sepsis, ischemia, and nephrotoxic models
Kidneys from sham-operated mice had alternating light and dark stripes in the cortex and outer medulla and the pelvis filled quickly with contrast (Fig. 1A), as described previously for normal mouse kidneys [13]. The contrast was cleared rapidly from the blood as evidenced by the darker appearance of the renal vessels at 17 minutes after injection of contrast agent (Fig. 1A). The appearance of the kidney 20 hours post-CLP was very different (Fig. 1B). The kidney was homogeneous without the striped appearance. Contrast was not seen in the pelvis and the vasculature remained “bright,” indicating that the contrast agent was not cleared from the blood (Fig. 1B).

Compared to controls, the mice that received furosemide and low sodium diet developed volume depletion and prerenal azotemia as evidence by weight loss (8.0 ± 0.7% for treated v 0.6 ± 0.8% for control) (N = 5) (P < 0.05) and elevated blood urea nitrogen (BUN) (38 ± 6 mg/dL for treated vs. 13 ± 1 mg/dL for control) (N = 5) (P < 0.05). The dendrimer-enhanced MRI scan of the kidney in all volume-depleted mice was indistinguishable from control but clearly different from the image 20 hours post-CLP. Figures 2A and 6B show a typical example of an image obtained after volume depletion. This mouse had a BUN of 54 mg/dL, 7% weight loss, and a renal failure index (urine sodium * plasma creatinine/urine creatinine) of 0.9%. The pattern following CLP (Fig. 2A) was also different from the pattern seen after 40 minutes renal ischemia/4 hours reperfusion (Fig. 2C) or 3 days after cisplatin administration (Fig. 2D). In both renal ischemia and cisplatin models, the outer medullary stripes were absent and there was a high signal intensity in the outer cortex that represented accumulation of contrast agent within the proximal convoluted tubules.
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Figure 2. Patterns of dendrimer-enhanced magnetic resonance imaging (MRI) in acute renal failure (ARF). MRI scans of the right kidney 17 minutes after intravenous injection of G4 dendrimer. (A) Volume-depleted mouse. (B) Cecal ligation and puncture (CLP)-operated mouse 20 hours postsurgery. (C) Kidney 4 hours after 40 minutes of ischemia. (D) Kidney 3 days after 400 μg of cisplatin intraperitoneally.

Figure 3 shows dendrimer-enhanced MRI scans from mice 20 hours after sham operation (Fig. 3A) or CLP (Fig. 3B). Also shown, in Figure 3C to F, are PAS-stained sections from the same kidneys as imaged in Figure 3A and B. When compared to sham-operated animals, there was vacuolar degeneration in the cortex and outer stripe of the outer medulla of the kidney post-CLP. This is consistent with the MRI scan demonstrating failure of contrast uptake in both cortex and medulla.

Surprisingly, at 6 hours post-CLP the image was already abnormal and similar to the appearance at 20 hours (Fig. 4). The kidney shows a low level of contrast agent uptake with no stripes or contrast agent in the pelvis when compared to sham. The MRI scan did not change during the 17 minutes of scanning (not shown).

Effect of ethyl pyruvate on dendrimer-enhanced MRI

We have previously demonstrated that ethyl pyruvate can prevent and treat sepsis-induced ARF [10].

Figure 5 shows the effect of ethyl pyruvate on the dendrimer-enhanced MRI scans following CLP in aged mice. As described above, 20 hours after CLP the kidney had a distinct homogenous appearance. When ethyl pyruvate was administered at 0 and 6 hours post-CLP, the MRI appearance at 20 hours was that of a normal mouse (i.e., outer medullary stripes with contrast in the pelvis) (Fig. 5B). However, the dendrimer-enhanced MRI scan at 6 hours was abnormal (Fig. 5A). There were no outer medullary stripes or contrast in the pelvis at 6 hours, but this appearance emerged by 20 hours.

Full body MRI scans were obtained 20 minutes after intravenous injection of contrast agent. Sham-operated mice and mice with prerenal azotemia cleared the contrast agent from the circulation into the bladder (Fig. 6A and B). This clearance was inhibited at 6 and 20 hours post-CLP (Fig. 6C and D). The contrast agent remained in the blood pool resulting in high signal intensity in the vasculature. Ethyl pyruvate treatment of the CLP-operated mouse resulted in contrast agent clearance from the circulation 20 hours after surgery (Fig. 6E).

Dendrimer-enhanced MRI compared to serum creatinine

As previously reported, 20 hours post-CLP the serum creatinine level was increased and ethyl pyruvate inhibited this elevation in creatinine (CLP 20 hours 0.44 ± 0.05 mg/dL, CLP + ethyl pyruvate 20 hours 0.12 ± 0.01 mg/dL) (N = 8 per group) (P < 0.005) (Fig. 7A). At 6 hours post-CLP the serum creatinine was not significantly different from sham [sham 0.14 ± 0.01 mg/dL (N = 4), CLP 6 hours 0.17 ± 0.01 mg/dL (N = 8) (P > 0.05)]. The MRI scans were scored using a semiquantitative scoring system (see the Methods section). The MRI injury scores show that at 6 and 20 hours post-CLP the MRI scans were significantly different from sham (Fig. 7B). With ethyl pyruvate treatment the MRI scans at 6 hours, but not at 20 hours, were significantly different from sham (Fig. 7B).

Dendrimer-enhanced MRI and prognosis

To determine if the 6-hour MRI has prognostic value the size of the puncture hole in the CLP procedure was varied (Fig. 8). This produced a range of MRI injury scores at 6 hours post-CLP. As the MRI renal injury score increases the time to death was reduced (Fig. 8). Mice surviving to 7 days were imaged again with dendrimer-enhanced MRI. These images showed no renal abnormality (data not shown).

DISCUSSION

These studies demonstrate that dendrimer-enhanced MRI can distinguish sepsis-induced ARF from prerenal azotemia and renal failure due to I/R or cisplatin. The renal injury can be detected as early as 6 hours post-CLP, before serum creatinine is elevated. The effect of
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therapy can also be monitored as ethyl pyruvate treatment causes the MRI scan to return to a normal appearance at 20 hours, but not at 6 hours, post-CLP treatment. The detection of renal injury at 6 hours has prognostic power as it predicts survival time after sepsis.

**Dendrimer-enhanced MRI can distinguish between ARF due to different etiologies**

We found that the pattern of dendrimer-enhanced MRI after sepsis is quite different from I/R or cisplatin. In sepsis there is global renal dysfunction; cortical and medullary kidney cells fail to accumulate contrast agent whereas I/R (or cisplatin) causes a more selective outer stripe dysfunction. The MRI pattern is consistent with the location of histologic damage; the global reduction in renal dendrimer uptake after sepsis is paralleled by the cortical and medullary vacuolization observed in the renal histologic sections taken post-CLP. The selective outer stripe defect in I/R and cisplatin MRI images parallels the major site of histologic damage, the outer stripe of the medulla [16, 17]. Thus, dendrimer-enhanced MRI may predict the site of renal injury and sepsis-induced ARF is quite different from renal ischemia.

Sepsis is a common cause of ARF and had been previously modeled in rodents by I/R because both have low renal perfusion. However, evidence is now emerging that...
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Fig. 4. Dendrimer-enhanced magnetic resonance imaging (MRI) 6 hours after sepsis. MRI scans of the right kidney 17 minutes after intravenous injection of the G4 dendrimer. (A) Sham-operated mouse 6 hours after surgery. (B) Cecal ligation and puncture (CLP) mouse 6 hours after surgery.

Fig. 5. Effect of ethyl pyruvate on dendrimer-enhanced magnetic resonance imaging (MRI) following sepsis. MRI scans of the right kidney 17 minutes after intravenous injection of G4 dendrimer. (A) Cecal ligation and puncture (CLP) mouse treated with ethyl pyruvate at time 0. Image taken 6 hours after surgery. (B) CLP mouse treated with 14 mM ethyl pyruvate at time 0 and 6 hours after surgery. Image taken 20 hours after surgery.

ARF induced by sepsis is a distinct entity from ischemic ARF. In our CLP aged mouse model, ARF has a different histologic pattern of injury to I/R (vacuolization vs. necrosis) and a dramatic lack of inflammation [10]. The MRI data presented in this paper support the conclusion that sepsis and ischemia are distinct entities. To distinguish the cause of ARF without biopsy would be clinically useful as the cause of ARF is often obscure or multifactorial. To translate therapies which are effective in specific animal models to clinical treatments requires the recruitment of the correct patients into clinical trials. Existing protein biomarkers such as CYR61, KIM-1 or NHE3 are unable to distinguish sepsis from ischemia [10, 12, 18, 19]. Dendrimer-enhanced MRI may represent a valuable tool for correctly classifying the etiology of a patient’s ARF which might then improve the ability of a trial to correctly identify an effective treatment. The results presented here suggest that dendrimer-enhanced MRI may be useful in defining the insult producing ARF, especially when combined with clinical data and other biomarkers.

Dendrimer-enhanced MRI can detect renal dysfunction earlier than serum creatinine

Lack of an early disease marker for ARF has delayed timely recruitment of patients into clinical trials. After only 6 hours, dendrimer-enhanced MRI can demonstrate that sepsis produces changes in renal function. Even at this early time post-CLP the kidney is failing as evidenced by the lack of contrast agent uptake in the cortex, medulla, pelvis, and bladder. At this time point, serum creatinine is normal. Therefore, dendrimer-enhanced MRI can detect renal failure before serum creatinine is elevated. Previous studies have shown that other, more invasive indicators of renal injury are present 6 hours post-CLP. Histologic changes are present and the injury marker CYR61 is raised 6 hours post-CLP in aged mice [10]. Both of these methods require kidney tissue; dendrimer-enhanced MRI is the first noninvasive method of detecting ARF early after CLP. The MRI scans 6 and 20 hours post-CLP were different from the renal image obtained in prerenal azotemia induced by volume depletion. To distinguish prerenal azotemia from established ARF is important [20] and, thus, dendrimer-enhanced MRI is promising as a potential clinical biomarker. While renal hypoperfusion may contribute to the pathogenesis of sepsis-induced ARF, the different MRI scans suggest that ARF in our CLP model is not simply prerenal azotemia.

Dendrimer-enhanced MRI can track drug therapy

In developing new clinically useful therapies a biomarker which can track drug response would be valuable as an intermediate end point and greatly aid the determination of drug dosing. As reported previously, ethyl pyruvate prevents ARF in the aged mouse model of sepsis [10]. At 20 hours after induction of sepsis (by cecal ligation and puncture) the MRI scans appear normal with ethyl pyruvate treatment but abnormal with vehicle. This demonstrates that dendrimer-enhanced MRI can track effective drug treatment for sepsis-induced ARF. Dendrimer-enhanced MRI may prove to be superior to serum creatinine or even creatinine clearance as a tool to measure drug response. The MRI technique has faster kinetics than serum creatinine (6-hour MRI injury score vs. 6-hour serum creatinine concentration) and provides more direct information about kidney cell function (contrast agent uptake) and contrast agent excretion from the circulation.

In the CLP model of polymicrobial sepsis administration of agents such as ethyl pyruvate or antagonists of the cytokine HMGB1 can inhibit ARF even if started 6
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Fig. 6. Full-body dendrimer-enhanced magnetic resonance imaging (MRI) following sepsis. (A) Twenty hours after sham surgery. (B) Volume depletion. (C) Six hours after cecal ligation and puncture (CLP). (D) Twenty hours after CLP. (E) Twenty hours after CLP + ethyl pyruvate.

Fig. 7. The effect of ethyl pyruvate on serum creatinine and magnetic resonance imaging (MRI) after sepsis. (A) Serum creatinine values for sham- and cecal ligation and puncture (CLP)-treated mice. The CLP-treated mice had blood taken at 6 or 20 hours. CLP mice were also treated with ethyl pyruvate at time 0 and 6 hours postsurgery and blood taken at 20 hours. Data represent four to eight mice per group. *P = 0.029 vs. sham; + P = 0.005 vs. CLP 20 hours. (B) MRI injury scores for sham- and CLP-treated mice. The CLP-treated mice had images taken at 6 or 20 hours. CLP mice were also treated with ethyl pyruvate at time 0 and 6 hours postsurgery and images taken and 6 and 20 hours. Data represent four to eight mice per group. *P < 0.02 vs. sham; +P < 0.01 vs. CLP 20 hours. The creatinine and MRI data in (A) and (B) are from the same mice in each group.

Fig. 8. The relation between kidney magnetic resonance imaging (MRI) injury score at 6 hours post-cecal ligation and puncture (CLP) and survival time. Aged mice underwent CLP using a range of needle sizes for cecal puncture. The renal injury at 6 hours was defined by dendrimer-enhanced MRI. The mice received antibiotics and fluids twice daily and their survival monitored. Line shows linear regression ($r^2$ = 0.88).

to 24 hours after surgery [10, 21]. This implies that the MRI appearance at 6 hours is reversible. The pathophysiology underlying this is still unclear. The MRI pattern at 6 hours and 24 hours may represent the same process which is reversible at the earlier time point. Alternatively, multiple pathophysiologic mechanisms may develop over time, for example, different contributions from changes in renal blood flow, vascular and tubular processes occurring at different time-points. It is interesting that MRI of an early timepoint (6 hours post-CLP) fails to distinguish ethyl pyruvate-treated from vehicle-treated septic mice. This may suggest that the “drug target” for ethyl pyruvate becomes active between 6 to 24 hours post-CLP. Recently Yang et al [21] reported that serum HMGB1
Early MRI provides information about severity of illness and survival

By varying the needle size used for cecal puncture a range of renal injury at 6 hours post-CLP was produced. The resulting MRI scans varied from normal to complete absence of kidney stripes and contrast agent in the pelvis. The severity of the MRI scan at 6 hours correlated with the length of survival despite continued fluid and antibiotic treatment. Therefore, dendrimer-enhanced MRI can provide prognostic survival information. It is likely that survival after CLP in the mouse model depends on the function of multiple organs and the prognostic value of imaging the kidney may reflect the severity of multiorgan dysfunction. Indeed, at 6 hours post-CLP splenic injury could also be detected (data not shown). Human studies in the critical care setting have established that acute renal failure is a risk factor for death [5, 23, 24]. Therefore, dendrimer-enhanced MRI may be a prognostic marker by virtue of its ability to quantify renal contribution to the excess mortality in sepsis.

While this is data collected in the laboratory setting, imaging a septic patient early would be very valuable if outcome in the clinical setting could be predicted. While unlikely such an MRI technique would be used in routine clinical practice, very specific roles in clinical research projects and early phase clinical trials can be envisioned. One of the many remaining challenges is to develop a more practical biomarker(s) which can also detect ARF early, track drug treatment, and provide prognostic information. Ideally this biomarker would be easily measured in the serum or urinary proteome. Rapid developments in genomics and proteomics have provided new tools for biomarker discovery [25] and hopefully will be successfully applied to ARF. Dendrimer-enhanced MRI may be useful as a tool to carefully phenotype patients whose serum/urine will be subjected to proteomic analysis. Dendrimer-enhanced MRI may also provide important renal-specific severity of illness information that can not be obtained from serum creatinine because of the slow kinetics of creatinine in early ARF. Finally, dendrimer-enhanced MRI may be useful in phase 1 and early phase 2 studies as an intermediate ("surrogate") end point to better indicate therapeutic efficacy than standard tests of renal function.

CONCLUSION

Dendrimer-enhanced MRI is an effective biomarker for sepsis-induced ARF. It can detect renal injury early, provide information about the cause, track the response to therapy, and provide prognostic information. This initial study of dendrimer-enhanced MRI in a mouse model of sepsis-induced ARF supports this technique being further validated and developed as an independent biomarker and intermediate end point for human studies.

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