Arterial spin labeling blood flow magnetic resonance imaging for evaluation of renal injury

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Liu YP, Song R, Liang CH, Chen X, Liu B. Arterial spin labeling blood flow magnetic resonance imaging for evaluation of renal injury. Am J Physiol Renal Physiol 303: F551–F558, 2012.—A multitude of evidence suggests that iodinated contrast material causes nephrotoxicity; however, there have been no previous studies that use arterial spin labeling (ASL) blood flow functional magnetic resonance imaging (fMRI) to investigate the alterations in effective renal plasma flow between normotensive and hypertensive rats following injection of contrast media. We hypothesized that FAIR-SSFSE arterial spin labeling MRI may enable noninvasive and quantitative assessment of regional renal blood flow abnormalities and correlate with disease severity as assessed by histological methods. Renal blood flow (RBF) values of the cortex and medulla of rat kidneys were obtained from ASL images postprocessed at ADW4.3 workstation 0.3, 24, 48, and 72 h before and after injection of iodinated contrast media (6 ml/kg). The H&E method for morphometric measurements was used to confirm the MRI findings. The RBF values of the outer medulla were lower than those of the cortex and the inner medulla as reported previously. Iodinated contrast media treatment resulted in decreases in RBF in the outer medulla and cortex in spontaneously hypertensive rats (SHR), but only in the outer medulla in normotensive rats. The iodinated contrast agent significantly decreased the RBF value in the outer medulla and the cortex in SHR compared with normotensive rats after injection of the iodinated contrast media. Histological observations of kidney morphology were also consistent with ASL perfusion changes. These results demonstrate that the RBF value can reflect changes of renal perfusion in the cortex and medulla. ASL-MRI is a feasible and accurate method for evaluating nephrotoxic drugs-induced kidney damage.

iodinated contrast media; kidney perfusion; ASL-fMRI; contrast-induced nephropathy

CONTRAST MEDIA-INDUCED NEPHROPATHY (CIN) is administered for radiographic purposes and is said to be the third most common cause of hospital-acquired renal failure (15), accounting for 10–15% of total cases (6). The incidence of CIN is likely to increase with the wide use of spiral computed tomography (CT) imaging with intravascular contrast enhancement, including CT angiography and perfusion studies, as well as interventional cardiovascular procedures particularly in patients with compromised general health. Several mechanisms have been suggested to explain the pathogenesis of CIN, including blood flow changes, direct tubular toxicity, and intratubular obstruction (5, 9). Decreased renal plasma flow, a major determinant of glomerular filtration rate, is thought to play a key role in CIN (9). Notably, impaired kidney perfusion is recognized as being an important prognostic marker for the occurrence of a variety of morbidities, including renal diseases, hypertension, metabolic syndrome, diabetes, and atherosclerosis. However, it is still difficult to measure kidney perfusion in clinical trials.

In recent years, blood flow can be measured with a new magnetic resonance imagery (MRI) technique known as arterial spin labeling (ASL), which does not require the use of contrast agents (2, 10, 21, 24, 26). The flow-sensitive alternating inversion recovery (FAIR) of abdominal ASL can be very helpful at reducing background signal and subtraction errors (4, 17, 27). A combination of this background suppression strategy with the improved image quality provided by single-shot fast-spin echo (SSFSE) imaging could address most of the prior limitations of ASL in body imaging (3). FAIR with SSFSE sequence is sufficient to obtain perfusion-weighted images with good signal-to-noise ratio (7).

In this study, we hypothesized that FAIR-SSFSE ASL-MRI may enable noninvasive and quantitative assessment of regional renal blood flow (RBF) abnormalities and correlate with disease severity as assessed by histological methods. The purpose of our study was to determine the reliability and sensitivity of the quantitative renal perfusion parameter-RBF using ASL-fMRI in microvascular diseases and to validate those methods.

MATERIALS AND METHODS

Animals and Experimental Design

Sprague-Dawley (SD) rats (weighing 110.43 ± 13.75 g) and spontaneously hypertensive rats (SHR; weighing 120.01 ± 19.37 g) were anesthetized with an intraperitoneal injection of 20% urethane (6 ml/kg). During anesthesia, rectal temperature was monitored and body temperature maintained at 37 ± 0.5°C with a heating lamp. Animals were randomly divided into experimental or control groups. Experimental group rats received iodinated contrast agent (6 ml/kg) (1) via tail vein injection. At 0.3, 24, 48, and 72 h (22), and after injection the rats were scanned with MRI. Each rat was fasted for 4 h and without access to water before MRI scanning. The MRI scans of the rats were performed about 30 min after intraperitoneal anesthesia and after a smooth breathing pattern was achieved. At each time point, rats were euthanized to examine renal pathology.

All procedures were approved by the University Animal Care Committee and conformed to the Guide for the Care and Use of Laboratory Animals published by US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

MRI Protocol

Image acquisition. All experiments were performed on a 3.0T Sigma EXCITE HD/GE whole body scanner equipped with a 40 mT/m (200 mT/m-ms) gradient system and a transmit birdcage coil.
with 50-mm outer diameter for experimental investigations with animals. Rats were positioned supinely and vertically in a rotating cradle placed immediately in front of a stationary detector. MRI scans were performed 0.3, 24, 48, and 72 h after injection of iodinated contrast media. The routine sequence of T1WI and T2WI acquired anatomic images in axial and coronal planes. The functional images were acquired in coronal plane by ASL-FAIR-SSFSE sequence. In this experiment, ASL was performed using a background-suppressed multisection FAIR preparation and an SSFSE imaging sequence on a 3.0-T whole body imager. These parameters resulted in an acquisition time of 2.8 s per dynamic image (Fig. 1A).

Scan parameters. The FSE-XL/T1WI sequence was as follows: axial scan mode = 2D, grad mode = zoom, TR = 500 ms, TE = 13.3 ms, flip angle = 90°, bandwidth = 83.33 Hz, NEX = 4.0, FOV = 10.0 cm, slice thickness = 2.0 mm, sap = 0.2 mm, matrix = 288 × 192, ET = 3, scan time = 189 s.

The FSE-XL/T2WI sequence was as follows: axial and coronal scan mode = 2D, grad mode = zoom, TR = 3,500 ms, TE = 120 ms, bandwidth = 62.50 Hz, NEX = 8.0, FOV = 10.0 cm, slice thickness = 2.0 mm, sap = 0.2 mm, matrix = 288 × 192, ET = 19, scan time = 231 s.

The FAIR-SSFSE sequence was as follows: coronal scan mode = 2D, grad mode = zoom, TR = 2,453.3 ms, TE = 120 ms, bandwidth = 83.33 Hz, FOV = 10.0 cm, slice thickness = 2.0 mm, sap = 0.2 mm, matrix = 128 × 128, ET = 19, multislice = 4 slices, 80 imagings, scan time = 208 s.

Image analysis. Four-layer scanning was performed on each kidney, with 20 different images at each layer. All images were submitted to access renal perfusion images by Functool-Fair software on (Advantage Workstation 4.3 GE Medical System) ADW4.3. The FAIR perfusion measurement was performed as previously described (25). MRIs were evaluated by two radiologists blinded to the group designations. In case of a discrepancy in the results, a consensus was reached between the two radiologists. The blood flow values of cortex, outer medulla, and inner medulla were measured on renal perfusion imaging (Fig. 1B).

Fig. 1. Representative coronal MR image (A) and renal blood flow (RBF) map (B) of dynamic 3D gradient-echo perfusion sequence. The region of interest (ROI) tracing for each kidney represents the cortex (1), outer medulla (2), and inner medulla (3). The overlay image is propagated through appropriate dynamic series while manually correcting for kidney motion, which is repeated in 4 sections from each kidney. Software is configured to sum number of voxels and MR signal intensity, which can subsequently help determine blood flow of kidneys (Equation).

Fig. 2. Time course studies of RBF by T2WI MRI in normal rats over a 72-h period after injection of iodinated contrast media. Representative coronal single-shot fast spin-echo MR image shows cortex, outer medulla, and inner medulla of 4 sections of each kidney before iodinated contrast media infusion (A) and at 0.3 (B), 24 (C), 48 (D), and 72 h (E) after infusion.
Region of interest measurement. The region of interest (ROI) selected on each kidney of the same experimental subject had the same size and shape. Each ROI had the area of 1.5–2.5 mm² and contained at least five pixels; 6–10 ROIs were measured in cortex, outer medulla, and inner medulla. There were no distortions, artifacts, or large vessels in the ROIs.

Histological Assessment

Rat kidneys were harvested and immediately fixed in 10% buffered formalin after being washed with normal saline. The kidney specimens were prepared by alcohol dehydration, made xylene transparent, bapitst waxed, and paraffin embedded, after which time they were cut into 3-μm sections for conventional H&E staining. The specimens were blindly and randomly reviewed under ×200–400 magnification with use of a light microscope.

Statistical Analysis

Data were analyzed using SPSS for Windows. All values are expressed as means ± SD. Differences between groups were assessed by means of simple one-way analysis of variance and Student’s t-tests. P < 0.05 was considered to be statistically significant.

RESULTS

MRI

Three-dimensional perfusion images were obtained in all individuals without complication. The time response of RBF values in the left and right cortex and medulla in the rats with the iodinated contrast agent infusion is depicted in Fig. 2B, while Fig. 2A shows MRIs of ASL-FAIR-SSFSE and T2WI acquired in one rat. In the right kidney, the iodinated contrast agent significantly decreased the RBF value by 13.6, 13.9, and 7.9% (P < 0.05 vs. preinjection, n = 6, respectively; Table 1) at 0.3, 24, and 48 h postinjection, respectively, whereas at 72 h postinjection the contrast media only mildly reduced the RBF value by 3.6%. For the left kidney, the contrast media caused a significant decrease in the RBF value (P < 0.05) at 0.3, 24, and 48 h postinjection, respectively, whereas at 72 h postinjection the contrast media resulted in a mild decrease in the RBF value (Table 1). The RBF values of the outer medulla were lower than those of the cortex. The RBF value of the cortex and the medulla was not significantly different between the right and left kidneys.

To determine the effect of the contrast agent on damaged kidneys, we also observed changes in RBF in the SHR group following contrast agent infusion (Fig. 3). Interestingly, the RBF of the cortex and the outer medulla of the right and left kidneys were significantly decreased in a time-dependent manner postinjection of the contrast media (P < 0.05 vs. preinjection, n = 5, respectively; Table 2). In the inner medulla, the RBF value of both kidneys was significantly decreased 72 h postinjection (P < 0.05 vs. preinjection, n = 5, respectively; Table 2).

To further verify the potential of ASL-fMRI for evaluation of renal injury, we compared results from normal SD rats and SHR. Outer medulla RBF in SH rats were similar to those of normal rats prior to infusion (Fig. 4). Contrast infusion induced a significant, time-dependent decrease in RBF in both groups (P < 0.05; Fig. 4). However, the absolute decrease in RBF during contrast infusion was greater in the SHR group than in the normal SD group (P < 0.05; Fig. 4). Moreover, the value of RBF was recovered in normal rats compared with SHR.

### Table 1. RBF values in normal rat kidneys (mean ± SD)

<table>
<thead>
<tr>
<th>Position</th>
<th>Outer medulla</th>
<th>Inner medulla</th>
<th>Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>RBF (ml·min⁻¹·100 g⁻¹)</td>
<td>RBF (ml·min⁻¹·100 g⁻¹)</td>
<td>RBF (ml·min⁻¹·100 g⁻¹)</td>
</tr>
<tr>
<td>0 h</td>
<td>114.6 ± 7.39</td>
<td>96.71 ± 6.07</td>
<td>124.89 ± 6.60</td>
</tr>
<tr>
<td>0.3 h</td>
<td>108.60 ± 3.38</td>
<td>101.53 ± 9.60</td>
<td>105.34 ± 6.39</td>
</tr>
<tr>
<td>24 h</td>
<td>103.30 ± 3.38</td>
<td>111.56 ± 9.50</td>
<td>125.67 ± 9.16</td>
</tr>
<tr>
<td>48 h</td>
<td>96.34 ± 4.88</td>
<td>112.86 ± 9.00</td>
<td>126.30 ± 6.19</td>
</tr>
<tr>
<td>72 h</td>
<td>91.11 ± 9.42</td>
<td>95.79 ± 6.56</td>
<td>92.10 ± 6.01</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD in ml·min⁻¹·100 g⁻¹. Position indicates 3 renal regions: outer medulla, inner medulla, and cortex. SHR, renal blood flow; RBF, renal blood flow. RBF values were measured in the 3 renal regions: from right and left kidneys. *P < 0.01 vs. outer medulla.
This was further illustrated by the RBF value in the left outer medulla, which decreased 18.94% in the SHR group during the contrast infusion compared with a 16.44% decrease in the normal SD group (P < 0.05; t-test). The RBF values in the inner medulla and the cortex during stimulation were also significantly reduced in the SHR group, whereas there were no significant changes in the normal SD group.

Iodinated Contrast Agent-Induced Changes in Kidney Morphology

To further identify whether kidney injury was present following injection of iodinated contrast agents and allows correlation with disease severity, renal morphology was assayed using H&E staining. The number of normal glomeruli and normal vessels was decreased in all hypertensive animals (vs. normotensive animals). Normotensive animals showed signs of glomerular injury, including collapsing glomerulopathy, mesangial sclerosis, mesangiolysis, extracapillary proliferation, protein decreases, and especially high grade of glomerulosclerosis when compared with normotensive animals. Histological results of 0.3, 24, 48, and 72 h postinjection of iodinated contrast media are summarized and evaluated in Fig. 5 and Table 3. Slight kidney damage was evident following postinjection for 0.3 h, as indicated by congested, narrow, and disrupted proximal convoluted tubules with cloudy, swollen epithelial cells, necrotic debris, reduction of brush borders, and expansion of interstitium (Fig. 5A). In contrast, the kidneys of rats 24 h postinjection had greater morphological changes in the tubules as well as renal glomerular alterations and cellular swelling (Fig. 5B). At 48 h postinjection, atrophied glomeruli and tubular damage with fatty degeneration and hyaline degeneration were observed (Fig. 5C). However, the morphological changes in kidneys showed glomerular fibrosis and tubular damage without steatosis and hyaline degeneration 72 h postinjection (Fig. 5D).

In contrast, in the SHR group, the contrast induced a greater degree of glomerular and tubular damage, which was time dependent (Fig. 6 and Table 3). All nephrons with glomerular or tubular damage were localized in the juxtamedullary cortex. The associated tubule was acutely damaged, with flattened epithelium and detached epithelial cells in the tubular lumen. In the juxtamedullary cortex of SHR, there was greater glomerular injury, including collapsing glomerulopathy, mesangial sclerosis, mesangiolysis, extracapillary proliferation, protein decreases, and an especially high grade of glomerulosclerosis (Fig. 6) compared with normotensive animals with injection of the contrast. Telangiectasis and hyperemia in the renal glomerulus was greater in SH rats than in normotensive animals 72 h postinjection (Fig. 6D). Furthermore, there were no differences observed between the right and the left kidney of each animal after the contrast medium infusion.

DISCUSSION

To the best of our knowledge, this is the first study to quantify RBF with ASL imaging in kidneys with CIN with or without hypertension. Another important implication of this observation is that the impaired perfusion can translate into a grossly altered clinical course, as this study implicates good initial and damaged renal function. The application of ASL, an MRI method, in clinic patients has shown promise. ASL-fMRI
Table 2. RBF values in SHR kidneys ("mac/H9273/H11006/s)

<table>
<thead>
<tr>
<th>Position</th>
<th>Right RBF</th>
<th>Left RBF</th>
</tr>
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<tbody>
<tr>
<td>Outer medulla</td>
<td>0h: 101.58, 0.3h: 88.45, 2h: 90.39, 4h: 92.33, 8h: 89.61</td>
<td>0h: 108.11, 0.3h: 88.56, 2h: 90.47, 4h: 92.43, 8h: 89.80</td>
</tr>
<tr>
<td>Inner medulla</td>
<td>0h: 99.79, 0.3h: 88.57, 2h: 90.34, 4h: 92.32, 8h: 89.62</td>
<td>0h: 108.11, 0.3h: 88.56, 2h: 90.47, 4h: 92.43, 8h: 89.80</td>
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<tr>
<td>Cortex</td>
<td>0h: 108.11, 0.3h: 88.56, 2h: 90.47, 4h: 92.43, 8h: 89.80</td>
<td>0h: 108.11, 0.3h: 88.56, 2h: 90.47, 4h: 92.43, 8h: 89.80</td>
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</tbody>
</table>

Values are presented as means ± SD in ml·100 g⁻¹·min⁻¹. SHR, spontaneously hypertensive rats. RBF values were measured in the 3 renal regions from right and left kidneys. *p < 0.05 vs. outer medulla.

Contrast media can cause vasoconstriction in the renal medullary blood flow and is nearly hypoxic under normal condition. The renal medulla handles only 20% of blood flow and is nearly hypoxic under normal condition. At baseline conditions, SHR displayed a slight decrease in RBF in the outer medulla compared with normotensive controls (18). Interestingly, SHR were found to display significantly lower RBF in the cortex than the control group. This pathology could have been the direct result of peripheral elevation of blood pressure, since increased blood pressure in SHR rats causes the cortex injury, including glomerulosclerosis and proximal tubular damage leading to insufficient RBF autoregulation (16).

After injection of iodinated contrast agents, ASL-RBF values in the renal outer medulla were significantly decreased, with the lowest values occurring at 0.3 h and then gradually recovering after 24 h, whereas ASL-RBF values in the cortex and inner medulla varied slightly. Our study and previous studies (9, 13) support the hypothesis that intravenous administration of iodinated contrast agent results in decreased renomedullary blood flow. The renal medulla handles only 20% of blood flow and is nearly hypoxic under normal condition. Contrast media can cause vasoconstriction in the renal medul-
Fig. 4. Variation in RBF values in normal rats and SHR over a 72-h period after injection of iodinated contrast media. Flow curves were created on corresponding images (Figs. 3 and 4). Means ± SD of values from 4 sections of each kidney from 5 different animals. Experiments were repeated at least once. *P < 0.05, **P < 0.01 vs. outer medulla; #P < 0.05, ##P < 0.01 vs. control group (rats at hour 0) (t-test and 1-way randomized ANOVA). ΔP < 0.05, ΔΔP < 0.01 vs. SD.

Fig. 5. Micrographs showing histopathological changes induced by iodinated contrast media in normal rats. Representative photomicrographs of 8 sections of each kidney from 0 (A), 0.3 (B), 24 (C), 48 (D), and 72 h (E) postinjection of iodinated contrast agents (H&E, ×400 magnification). Black arrows indicate tubules with narrowing, necrotic debris or cast formation; arrowheads indicate glomerulus swelling, atrophy, or fibrosis.
lary vasculature. Moreover, the contrast seemed to directly decrease renal medullary blood flow by increasing plasma viscosity and led to increased viscosity of tubular fluid, which further compromised renal medullary hemodynamics and may have added to impaired renal medullary blood flow. To evaluate the correlation of our RBF values obtained by ASL-fMRI with disease severity, we used histological methods. RBF values were found to correlate closely with the histopathological results (Figs. 5 and 6), but RBF values exhibited a higher degree of sensitivity. Not detected by our ASL imaging results were severe histopathological changes characterized by dilated and disrupted tubules with necrotic debris, great expansion of interstitium, increased interstitial cells, and reduction of brush borders in both normotensive and hypertensive rats. However, there were pathological changes observed in kidneys from SH rats 0.3 and 24 h postinjection of iodinated contrast agents compared with normotensive rats. Moreover, the glomerular and tubular damage was greater in kidneys from SH rats than in normotensive rats 48–72 h postinjection of iodinated contrast agents. The results are consistent with previous studies by Ueda et al. (23), who found that early and enhanced diuresis is associated with swelling of the renal parenchyma, presumably due to tubular luminal expansion and increased interstitial volume. Our results suggest that iodinated contrast agents caused renal hemodynamic changes and direct renal toxicity. Injection of iodinated contrast agents could lead to short renal vessel expansion and increases in blood flow followed by continuous renal vasoconstriction and less renal perfusion. RBF analysis by ASL-fMRI is effective in determining the extent of renal injury. Therefore, this study showed that ASL-RBF values could be used as an effective method for quantitative monitoring of renal perfusion clinically.

In this study, we used ASL-fMRI to measure renal regional perfusion. The perfusion map indicated significant differences in regional blood flow between renal cortex and medulla. It should be mentioned that the regions of interest for evaluation of perfusion rates were defined interactively to avoid large vessels and regions close to the transition to other types of tissue. Regions with reduced perfusion can be effectively evaluated using the FAIR SSFSE approach. Recent studies have found qualitative agreement between MRI-ASL and scintigraphy with respect to kidney perfusion measurement (14, 25). MRI-ASL methodology is advantageous compared with other methods to measure kidney perfusion due to the speed of analysis (within a few minutes) and its noninvasive nature (11, 20). The fact that ASL evaluations do not involve exogenous contrast medium bestows several benefits and opportunities for renal regional blood flow assessment. Moreover, assumptions

### Table 3. Evaluation of renal morphological damage

<table>
<thead>
<tr>
<th>Localization</th>
<th>SD (0 h)</th>
<th>0.3 h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
<th>SHR (0 h)</th>
<th>0.3 h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
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<tr>
<td>Glomerular damage</td>
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<tr>
<td>Parietal epithelial cell hypertrophy</td>
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<td>-</td>
<td>+</td>
<td>++</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Extracapillary proliferation</td>
<td></td>
<td>-</td>
<td>-/+</td>
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<tr>
<td>Fibrosis</td>
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<td>Tubular damage</td>
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<td>Focal atrophy</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
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<td>Casts</td>
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</table>

Kidney sections were stained with hematoxylin-eosin. SD, Sprague-Dawley rats. Morphological lesions were graded from – to 3+ (–, no changes; 1+, changes affecting <25% of sample; 2+, changes affecting 25–50% of sample; 3+, changes affecting 51–75% of sample).

Fig. 6. Micrographs showing histopathological changes induced by iodinated contrast media in SHR. Representative photomicrographs of 8 sections of each kidney from 0 (A), 0.3 (B), 24 (C), 48 (D), and 72 h (E) postinjection of iodinated contrast agents (H&E, ×400 magnification).
regarding the distribution of contrast media and the relationship between signal intensity and tracer concentration are bypassed with ASL.

In conclusion, our study demonstrated that ASL at 3.0T MRI yields high-quality quantitative renal perfusion imaging. Renal plasma flow measurements using MRI-ASL were capable of approximating changes in kidney perfusion. ASL-1MRI might be an attractive candidate for rapid, accurate, and noninvasive measurement of renal regional blood flow and for monitoring renal impairment in cases such as CIN in clinical practice.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: Y.L. and R.S. conception and design of research; Y.L., R.S., X.C., and B.L. performed experiments; Y.L., R.S., C.H.L., X.C., and B.L. analyzed data; Y.L., R.S., and C.H.L. interpreted results of experiments; Y.L. and R.S. prepared figures; Y.L. and R.S. drafted manuscript; Y.L., R.S., and C.H.L. edited and revised manuscript; Y.L., R.S., C.H.L., X.C., and B.L. approved final version of manuscript.

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