Hemodynamic Effects of Furosemide on Renal Perfusion as Evaluated by ASL-MRI

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Rationale and Objectives: The aim of this study was to investigate the short-term effects of furosemide on renal perfusion by using arterial spin labeling (ASL) magnetic resonance imaging.

Materials and Methods: Eleven healthy human subjects were enrolled in the study. The measurement of renal blood flow (RBF) was performed by applying an ASL technique with flow-sensitive alternating inversion recovery spin preparation and a single-shot fast spin-echo imaging strategy on a 3.0-T magnetic resonance scanner. For all subjects, the ASL magnetic resonance images were obtained before agent injection as a baseline scan. Then 20 mg of furosemide was injected intravenously. Postfurosemide ASL images were acquired following administration to evaluate the renal hemodynamic response.

Results: Postinjection scans showed that cortical RBF decreased from 366.59 ± 41.19 mL/100 g/min at baseline to 314.33 ± 48.83 mL/100 g/min at 10 minutes after the administration of furosemide (paired t test, \( P = .04 \) vs baseline), and medullary RBF decreased from 118.59 ± 24.69 mL/100 g/min at baseline to 97.38 ± 18.40 mL/100 g/min at 10 minutes after the administration of furosemide (paired t test, \( P = .01 \) vs baseline). There was a negative correlation between the furosemide-induced diuretic effect and the reduction of RBF (Spearman’s \( r = -.61 \)).

Conclusions: The dominant hemodynamic effect of furosemide on the kidney is associated with a decrease in both cortical and medullary blood perfusion. Furthermore, the quantitative ASL technique may provide an alternative way to noninvasively monitor the change in renal function due to furosemide administration.

Key Words: Arterial spin labeling; furosemide; renal blood flow; autoregulation.

Furosemide, a powerful diuretic acting on the thick ascending limb of the loop of Henle to promote the renal excretion of both water and solutes from the body, is commonly used in patients with congestive heart failure or oliguric acute renal failure (1–4). Like other loop diuretics, furosemide exerts its action by inhibiting NKCC2, the luminal \( \text{Na}^+\text{K}^+\text{Cl}^- \) cotransporter in the thick ascending limb of the loop of Henle (5). It has also been reported that loop diuretics inhibit NKCC1 (5). As the other isoform of the \( \text{Na}^+\text{K}^+\text{Cl}^- \) cotransporter, NKCC1 is widely expressed in the vasculature. The inhibition of NKCC1 by loop diuretics may produce direct vascular effects such as vasodilation in most vasculatures.

The well-established mechanisms of \( \text{Na}^+\text{K}^+\text{Cl}^- \) cotransporters suggest that the vascular effects of loop diuretics in the kidney should include vasodilatation (6). However, data from previous studies of the renal hemodynamic effect of furosemide are conflicting and difficult to reconcile. The expected increase of renal blood flow (RBF) induced by loop diuretic administration has been monitored in several studies in humans (7) and dogs (8). In contrast, in some rat or mice experiments, prominent reductions in RBF were observed (9–11). Moreover, the previously established data were performed mostly in anesthetized animals or by invasive facilities, which possibly upset the true actions of loop diuretics on renal autoregulation. Given these irreconcilable contradictions and the clinical importance of this class of drugs, it would be useful to achieve a better understanding of the mechanisms that may underlie the response of the renal vasculature to loop diuretics.

In recent years, noninvasive arterial spin labeling (ASL) magnetic resonance (MR) imaging (MRI) has been reported to be able to obtain reliable quantitative renal perfusion by tagging arterial water as an endogenous tracer agent (12–15). The aim of this study was to quantify the functional response to the intravenous administration of a loop diuretic, furosemide, in...
11 resting conscious young human subjects using ASL MRI. We hypothesized that this noninvasive technique would be sensitive to renal hemodynamic changes following furosemide injection, which would result in an expected change in perfusion throughout the kidney. As such, it is hoped that this noninvasive MR approach will be a prominent tool to study the functional characteristics of the kidney.

**MATERIALS AND METHODS**

**Human Subjects and MR Protocols**

Eleven healthy young volunteers (six men, five women; age range, 22–39 years) without histories of renal disease participated in this study. The subjects were asked to abstain from food and drink for about 12 hours overnight before participating in the study. After the study content was explained, the volunteers gave written informed consent according to a protocol approved by the local university ethics committee.

Experiments were conducted using a 3.0-T whole-body MR scanner (Signa Excite; GE Medical Systems, Milwaukee, WI) with a commercial Torso PA coil (GE Medical Systems). A gradient-echo sequence in three oblique planes through the center of the kidney was used for scout images. ASL acquisitions were performed for RBF measurements using a flow-sensitive alternating inversion recovery (FAIR) sequence combined with single-shot fast spin-echo imaging. A single oblique coronal plane through the center of both kidneys was determined with the following imaging parameters: repetition time, 3500 ms; echo time, 60 ms; flip angle, 90°; bandwidth, 62.5 kHz; slice thickness, 5 mm; matrix size, 128 × 128; and field of view, 40 cm². The slab thickness for section-selective inversion in the FAIR preparation was 30 mm, to avoid artifacts from not fully inverted spins at the margins of the readout slice. Six ASL images were obtained at the same slice position, three with section-selective inversion and three with global inversion, and averaged to generate two FAIR images with an inversion time (TI) of 1400 ms. M₀ images were acquired using single-shot fast spin-echo without FAIR preparation, the imaging parameters of which were same as for the FAIR single-shot fast spin-echo sequence described above, while the repetition time was set to 6000 ms to ensure a complete relaxation of the spins between measurements. To avoid motion artifacts, subjects were trained to hold their breath for 20 to 30 seconds each interval. The total measurement time for one slice was within 1 minute.

All subjects were asked to urinate before the MR examination. The ASL images were acquired before furosemide injection to obtain baseline measurements. Twenty milligrams of furosemide was then injected intravenously. Postfurosemide ASL images were acquired starting about 10 minutes following administration to measure the hemodynamic response. Because ASL may be influenced by different factors (ie, blood pressure, blood volume, hematocrit, and water content), three consecutive ASL images were recorded in both the preinjection and postinjection periods in each subject. The RBF values of prefurosemide and postfurosemide (postfurosemide) were averaged respectively as a single pair comparison. The diuretic effects of furosemide infusion were tested using a subjective urination score from subjects. Each subject was asked to record the feeling of urination 15 to 20 minutes after furosemide administration; urination scores ranged 0 from 10, where 0 represents no feeling to urinate and 10 represents an urgent feeling to urinate.

**Quantitative Analysis of MR Perfusion Data**

A quantitative model for the analysis of RBF using FAIR techniques has been previously described using the extended Bloch equations (16). The use of this model enables one to simulate the difference in longitudinal magnetization, ΔM(TI), between FAIR experiments with global preparation and those with section-selective preparation:

\[ ΔM(TI) = M_{sel}(TI) - M_{nonsel}(TI) = 2M₀TI\frac{f}{k}e^{-TI/T₁}, \]

where ΔM is the difference in magnetization between section-selective (M_{sel}) and nonselective (M_{nonsel}) measurements, M₀ represents the tissue equilibrium magnetization per unit mass of the tissue, T₁ is the longitudinal relaxation time of tissue, f is the perfusion rate (usually expressed in milliliters per 100 grams per minute), and k is the blood-tissue water partition coefficient, which is thought to be nearly constant at 0.80. Perfusion maps can be calculated pixel by pixel by analyzing ΔM at a given TI, M₀, and T₁ using the following equation:

\[ f = \frac{λ \cdot ΔM(TI) \cdot M₀}{2 \cdot T₁ \cdot M₀}e^{TI/T₁}. \]

ASL images were postprocessed using in-house MATLAB software (The MathWorks, Inc, Natick, MA), which allowed a nonlinear image registration to avoid RBF quantification errors due to motion artifacts (17). Motion-corrected MR images with section-selective and global inversion collected in two sets were averaged and subtracted to obtain the final ΔM images. The T₁ values for the cortex and medulla were set at 1142 and 1545 ms, respectively (18,19). Pixels with high perfusion of >600 mL/100 g/min in the cortex or >250 mL/100 g/min in the medulla were excluded from the RBF evaluation. Region-of-interest (ROI) analysis was used to calculate regional RBF. The M₀ image can provide the renal anatomic information to facilitate placement of the ROIs. Quantitative RBF covering the entire cortex was obtained by manually drawing its contour on the M₀ image. Given medullary RBF, five to six small ROIs were manually placed in the medullary compartments. The RBF values of these regions were then averaged (Fig 1). Similar ROI...
locations were used for all of the perfusion maps in the process of evaluating both pre-furosemide and post-furosemide RBF.

**Statistical Analysis**

Descriptive statistics (mean ± standard deviation) are used to summarize all variables. A two-tailed paired *t* test was used to determine the differences of RBF between the cortex and the medulla for pre-furosemide and post-furosemide. To investigate the correlation between hemodynamic and diuretic effects of furosemide infusion, the percentage RBF change between pre-furosemide and post-furosemide (P-RBF) was calculated, and the diuretic effect was graded according to urination scores: grade 1, scores of 0 to 4; grade 2, scores of 5 to 7; and grade 3, scores of 8 to 10. One-way analysis of variance with Fisher’s least significant difference test was then used. For the *t* test and analysis of variance, *P* values < .05 were considered to indicate statistically significant differences.

**RESULTS**

All subjects successfully completed the entire protocol. Three volunteers failed to sustain the breath-hold well during the scanning period, which resulted in severe motion artifacts. These three pairs of kidney ASL images were registered with the proposed nonlinear method, and the corrected RBF maps approached the quality of the images without motion artifacts (Fig 2).

Table 1 summarizes the hemodynamic response of kidney cortex and medulla to the furosemide administration. Post-furosemide scans showed that both cortical and medullary RBF was prominent decreased (paired *t* test, *P* = .04 for the cortex and *P* = .01 for the medulla vs baseline). Figure 3 shows the mean and intersubject deviations of RBF between pre-furosemide and post-furosemide.

Also, furosemide produced a relatively larger reduction in RBF in the medulla (P-RBF = −16.73 ± 11.73%) than in the cortex (P-RBF = −13.81 ± 12.92%), but the results did not reach statistical significance. A gender-dependent *t* test showed that furosemide did not produce a statistically significant difference in P-RBF between men and women (Fig 4).

With regard to the correlation between RBF reduction and the diuretic effect of furosemide, Spearman’s test revealed a good correlation between P-RBF and urination score (*r* = −0.61). Figure 5 shows that the higher the diuretic grade, the larger the reduction in RBF, and the results for P-RBF reached statistical significance in different diuretic grades (analysis of variance, *P* < .05).

Figure 6 shows two representative cases of the hemodynamic effects of furosemide on renal perfusion. Case 1 was a 22-year-old woman whose urination score was 8. The pre-furosemide versus post-furosemide RBF maps showed that cortical perfusion was mildly decreased, while medullary perfusion, as shown in the right kidney (arrow), was markedly reduced. In case 2 (a 25-year-old woman with a urination score of 6), furosemide produced a significant reduction of blood perfusion in both the renal cortex and the medulla.

**DISCUSSION**

Evaluation of the hemodynamic effects of loop diuretics on the renal vascular system is critical to clinical management (20,21). By applying noninvasive ASL MRI, we have demonstrated in the present study that the loop diuretic furosemide produces dominant reductions in both cortical and medullary RBF in normal young human subjects. Also, our data show that there is a good correlation between furosemide-induced diuretic effects and reductions of RBF.

Although ASL MRI is already prevalently used and valuable for the detection of acute vascular lesions in patients presenting with stroke symptoms (22–26), its application in abdominal organs is challenging because of respiration, peristalsis, and magnetic susceptibility artifacts. In recent years, there has been significant progress in ASL MRI application to the kidney (27–30). According to this in vivo study in 11 young volunteers, we revealed that it is feasible to monitor the hemodynamic effects of a loop diuretic, furosemide, on human renal function on the basis of sequential ASL MRI. By using a nonlinear image registration method to correct for respiratory movements, we were able to obtain RBF maps almost free of motion artifacts. As previously reported, our results showed that RBF can be reliably measured by repeated measurements on ASL MRI. The mean values of baseline RBF in this study were 366.59 ± 41.19 mL/100 g/min in the cortex and 118.59 ± 24.69 mL/100 g/min in the medulla, which were
consistent with those recently reported by Winter et al (31). However, the stability of ASL for the measurement of RBF depends on multiple factors, mainly concerning the intrinsic variability of blood pressure, blood volume, hematocrit, and water content, among others. Thus, in this study, ASL imaging was consecutively repeated three times (over a 3-minute time course) for prefurosemide and postfurosemide, and the RBF values were averaged to avoid time-dependent variation.

It is well established that furosemide has a direct effect on electrolyte reabsorption in the ascending limb of the loop of Henle, but its reported effect on renal hemodynamics has remained an issue of contradiction. As early as in 1966, Hook et al (11) detected a significant increase in RBF after the infusion of two loop diuretics, furosemide and ethacrynic acid. With the use of an electromagnetic flow meter, similar results were found by Ludens et al (32) in 1968. Moreover, they demonstrated that the capacity of furosemide to elevate RBF could be related to the initial resistance of certain vascular segments within the kidney; the higher the initial resistance in such segments, the greater the effect of this agent on RBF.

And this conclusion was confirmed by Duchin et al (33) in 1977. However, conflicting results were reported in rat experiments by Dobrowolski et al (12) in 2000, Janssen et al (13) in 1994, and Oppermann et al (15) in 2007. In most of these studies, furosemide was found to cause a remarkable increase in renal vascular resistance that produces a 10% to 20% reduction in RBF. Our results showed that furosemide produced a 13.81% reduction in cortical RBF and a 16.73% reduction in medullary RBF.

The renal hemodynamic response to furosemide may depend on RBF autoregulation. RBF autoregulation has been extensively investigated in previous studies. As described in many reviews of the literature (34–37), RBF autoregulation is based on two mechanisms, the myogenic response and tubuloglomerular feedback (TGF) (38,39). The myogenic response is known as the ability of vascular smooth muscle to constrict during an increase in intravascular pressure and to dilate upon a lowering of intravascular pressure. TGF is a more complicated control system specific to the kidney in which the tension of afferent arterioles is inversely regulated by the rate of delivery of tubular fluid to the more distal nephron segment. It has been reported that under resting conditions, the myogenic response contributes 0% to 50% to overall RBF autoregulation, TGF 35% to 50%, and the third mechanism 0% to 15% (37). Furosemide is prevalently identified with the ability to decrease renal vascular resistance and increase RBF by inhibiting TGF. However, the action of loop diuretics on RBF autoregulation is also probably

| TABLE 1. Changes in RBF from before to after Furosemide Infusion |
|---|---|
| Cortex | Medulla |
| Prefurosemide | Postfurosemide | Prefurosemide | Postfurosemide |
| 366.59 ± 41.19 | 314.33 ± 48.83* | 41.19 | 97.38 ± 18.40 |
| (n = 11 × 2) | (n = 11 × 2) | | |
| RBF (mL/100 g/min) | | |

*P < .05 (two-tailed paired t test).

P < .01.
influenced by initial renal perfusion pressure (32,40), animal or human species, gender, or age (41). It was found that loop diuretics produced an excessive generation of angiotensin II and vasoconstrictor prostaglandin in Oppermann et al’s (15) study, which suggests that the changes in both renin and prostaglandin activity may play an important role in

Figure 3. Effect of furosemide on renal perfusion. Shown are mean (a) and individual changes in cortical (b) and medullary (c) renal blood flow (RBF) after furosemide administration in 11 healthy young volunteers. Cortical and medullary RBF was prominently decreased at 10 minutes after furosemide administration.

Figure 4. Plots of decreased percentages of renal blood flow (P-RBFs) caused by furosemide between the cortex and the medulla (a) and the hemodynamic effect of furosemide between genders (b).

Figure 5. Relationship between percentage of renal blood flow (P-RBF) and diuretic effect. Spearman’s test showed a good correlation between P-RBF and urination score ($r = -0.61$) (a), and analysis of variance showed that results for P-RBF reached statistical significance in different diuretic grades (b).
The powerful diuretic action of furosemide to promote the renal excretion of water from the body will result in a remarkable decrease in renal blood volume and in turn leads to a decrease in RBF. Moreover, as the diuretic action of furosemide, the water and sodium freely filtered by the glomeruli and poorly absorbed by the renal tubule are able to abruptly increase tubular pressure, which leads to the compression of neighboring veins. ASL as used in this study is a flow-sensitive protocol that depends not only on the blood flow in arterial vessels but also that in venous vessels. Thus, even a short-term increase in proximal tubular pressure would probably decrease the measure of ASL RBF. Our data revealed a good correlation between furosemide-induced decrease in RBF and its diuretic effect. Although we note the limitation of this correlation, one may explain this result as indicating an influence of diuresis on RBF. As mentioned above, the reason could be a compression of peritubular veins by the rapid rise in tubular pressure. This mechanism would be effective, as the compression of peritubular capillaries caused by furosemide has been observed recently by a fluorescence microscopy in rat kidneys (42). And the blood flow reduction caused by furosemide was significantly improved after decapsulation, which was associated with less increase of proximal tubular pressure.

This study had some limitations. We referred to an established standard of renal $T_1$ relaxation time and assumed it to be unchanged with the administration of furosemide. However, it is worth mentioning that the water content in renal parenchyma was increased by 2% to 5% with furosemide administration in a rat experiment (43), which implies that the $T_1$ relaxation time may be influenced by furosemide. The effects of changed $T_1$ values on RBF estimation are currently unclear. Further study should be carried out on this issue.

CONCLUSIONS

Using a noninvasive ASL MRI, we concluded that the dominant hemodynamic effect of furosemide on the kidney is associated with a decrease in blood perfusion. Although its mechanism is not fully understood, clinicians should pay attention to its potential deleterious effect on some patients with renal insufficiency, as decreased renal blood perfusion implies more risk for acute renal failure in these patients.

REFERENCES