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Continuous prospectively navigated multi-echo GRE for improved BOLD imaging of the kidneys

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Abstract

Purpose: To develop improved methods for renal BOLD imaging. T2* mapping of the kidneys, or renal BOLD (blood oxygenation level dependent) imaging, may depict renal oxygen levels and may be valuable as a non-invasive means of following the progression of renal disease. Current renal BOLD data is limited by imaging in a single breath hold, which results in low resolution and low SNR. We compare a new free-breathing renal BOLD method with conventional breath hold BOLD.

Methods: A multi-echo GRE sequence with continuous prospective respiratory navigation and real-time feedback was developed that allows high resolution and high SNR renal BOLD imaging with constant sequence repetition time (TR) during free breathing (FB-BOLD). The sequence was evaluated in 10 normal volunteers and compared to conventional breath hold BOLD (BH-BOLD). Scan time for the FB-BOLD sequence was about 3:00 minutes, compared to 15 seconds for the BH-BOLD sequence. SNR of source images and residual error of T2* fitting were compared between the two methods.

Results: The FB-BOLD sequence produced motion-free T2* maps of the kidneys with SNR 1.9 times higher than BH-BOLD images. Residual error of T2* fitting was consistently lower in the right kidney with FB-BOLD (30% less than BH-BOLD) but higher in the left kidney (80% more than BH-BOLD), likely related to placement of the navigator on the right hemidiaphragm.

Conclusion: A free breathing prospectively navigated renal BOLD sequence allows flexible tradeoff between scan time, resolution, and SNR.

Graphical Abstract:

Renal BOLD MRI may be useful to depict oxygen levels in the kidneys, but is currently limited by the necessity of imaging in a single breath hold. A new method of renal BOLD MRI allows free breathing during image acquisition, providing flexible tradeoff of imaging time vs. quality. The new method was compared to existing methods and shown to improve signal-to-noise ratio of renal BOLD source images.

Keywords

renal BOLD MRI; T2* mapping; prospective navigation; real-time feedback

Introduction

A new method of renal BOLD (blood oxygen level dependent) MRI with continuous prospective navigation during free breathing has been developed to improve the accuracy of evaluation of oxygen levels in the kidney. Non-invasive measurement of kidney oxygen levels may be useful in many clinical scenarios, including chronic kidney disease (CKD). CKD afflicts 15% of the population in the United States. People with CKD have a mortality rate 2.4 times higher than those with healthy kidneys and are hospitalized 2.5 times more frequently. The annual cost of health care in the U.S. for patients with CKD totals about \$64 billion. CKD progresses to end stage renal disease (ESRD). Almost 600,000 people in the United States suffer from ESRD, requiring regular treatment with dialysis or kidney transplant in order to survive. Together, patients with CKD or ESRD account for \$98 billion in health care costs, about 20% of total health care expenditures in the US (1). These costs are expected to continue to grow.

Causes of kidney disease include diabetes, hypertension, and glomerulonephritis, which all converge to the common pathway of chronic kidney disease. Hypoxia is thought to be an important correlated and causative factor in the progression of chronic kidney disease to end stage renal failure (2–6). As chronic kidney disease worsens, the number of capillaries in the peritubular capillary bed within the renal medulla decreases (7), resulting in decreased medullary oxygen tension. This in turn contributes to the activation of a complex array of cytokines and other factors leading to tubulointerstitial fibrosis and impaired renal function (8), which is the hallmark of CKD. New therapies for the treatment of CKD that aim to correct renal hypoxia or ameliorate its effects are on the horizon (9–12). Pharmacologic agents can prolong the half-life of hypoxia inducible factors (HIFs) in the kidney, transcription factors that are increased in renal hypoxia and are protective against cellular damage (12). A noninvasive imaging test that could quantify renal hypoxia would have wide potential application in following the progression of chronic kidney disease and monitoring response to therapy, and might also be useful in predicting the development of kidney disease or detecting it at a preclinical stage.

The transverse relaxation time constant $T2^*$ is shortened in the presence of deoxyhemoglobin. Many factors in addition to oxygen concentration affect $T2^*$ in the kidneys, including physiologic variables such as tissue water content, perfusion, hematocrit, and vessel volume (13), and technical variables such as SNR, resolution, and motion artifact. Nevertheless, $T2^*$ mapping of the kidneys (renal BOLD imaging) may offer insights into the oxygenation level within the kidneys in health and disease. Published renal BOLD data has been variable, with several studies showing correlation between absolute cortical $T2^*$ values or change in $T2^*$ with diuresis with degree of CKD, while some studies show no association (14–27).

Limitations of the underlying MR methods may contribute to inconsistencies in published renal BOLD results. Because the kidneys move with respiration, renal BOLD data have mostly been based on single slice single breath hold images. The short imaging time (~20 seconds) necessary for breath holding results in poor spatial resolution and low SNR, both of which decrease the accuracy of $T2^*$ quantification.

To improve the accuracy of T2* estimation in the kidneys, we have developed a renal BOLD pulse sequence which allows free breathing and reduces respiratory motion artifact by a prospective navigation method. This method can be used to improve the SNR of 2D renal BOLD imaging. We compare this new method to conventional 2D breath hold BOLD to investigate source image SNR and goodness of T2* fit.

Experimental

Our new free breathing BOLD (FB-BOLD) sequence runs with constant repetition time (TR) and produces multi-echo gradient-recalled echo (GRE) images for T2* estimation. Prospective navigation (defined below) and real-time feedback are used to reduce motion artifact and allow imaging during free breathing. Imaging time can be lengthened beyond a single breath hold and flexibly traded off for increased resolution and SNR.

Prospective navigation and definition of navigator bins

Navigation is the rapid collection of a small amount of data which can be used to detect motion to direct subsequent data acquisition. In our new FB-BOLD sequence, navigation is performed by excitation of a slice oriented in the sagittal plane intersecting the diaphragm, with subsequent readout along the vertical axis. Fourier transform reconstruction gives the navigator echo, a one-dimensional projection of the slice along the readout direction. Signals from multiple receiver coils are separately reconstructed and then combined as a sum of squares to give a single one-dimensional magnitude navigator echo. A navigator echo is obtained at the beginning of each sequence repetition. This echo is processed in real time to determine its similarity to the navigator echoes from previous acquisitions, in order to sort the data into separate bins corresponding to different time points in the respiratory cycle. This method differs from conventional respiratory navigation by having constant TR necessary for BOLD imaging; conventional respiratory navigation interrogates the position of the diaphragm over and over and waits until diaphragm position is within an acceptable range to execute the actual imaging pulse sequence, resulting in variable TR. Our method is also different than conventional retrospective binning in which sequence TR is constant but navigators are analysed only after data acquisition, typically resulting in portions of k-space being redundantly overacquired while other portions are missing.

In our real-time prospective navigation, each bin is represented by a “reference echo.” The first navigator echo, obtained at the start of the first sequence repetition, is the reference echo of the first bin. The navigator echo from the next sequence repetition is compared to this first reference echo. If it is sufficiently similar to the first reference echo, the k-space line acquired during this sequence repetition will belong to the k-space of the first bin. If the new navigator echo is not similar to the first reference echo, a second bin is created and the new navigator echo becomes the reference echo representing this second bin. Similarly, navigator echoes from subsequent repetitions are compared to the reference echoes representing existing bins. If a new navigator echo is not sufficiently similar to any of the reference echoes representing existing bins, a new bin is defined with the new navigator echo as its reference echo.

In our current implementation, we perform phase encoding centrically within each bin. When one bin has a complete k-space, the imaging sequence is finished, and a motion-free image is constructed from the data in that bin. The other bins also contain data adequate for construction of images corresponding to other time points in the respiratory cycle, with lower resolution corresponding to their incomplete centrically-filled k-spaces. The prospectively navigated renal FB-BOLD imaging sequence is illustrated in Figure 1.

Real-time analysis of navigator echo to determine current k-space bin

Each navigator echo is normalized so that the sum of the squares of the points in the navigator echo is equal to 1, i.e.

$$\mathbf{nav}_{norm,i} = \frac{\mathbf{nav}_i}{\|\mathbf{nav}_i\|}.$$

where $\mathbf{nav}_i$ is the navigator echo obtained at the beginning of the i^{th} sequence repetition. The normalized navigator echo is compared sequentially to each of the normalized reference echoes defining existing bins. The similarity of the new navigator echo to existing reference echoes is quantified by the dot product of the two echoes

$$corr_{i,j} = \mathbf{nav}_{norm,i} \cdot \mathbf{nav}_{ref,j}$$

where $\mathbf{nav}_{norm,i}$ is the new navigator echo and $\mathbf{nav}_{ref,j}$ is the j^{th} reference echo. Because all of the navigator echoes have been normalized, $corr_{i,j}$ is always less than or equal to 1. If the correlation $corr_{i,j}$ between the new i^{th} echo $\mathbf{nav}_{norm,i}$ and an existing reference echo $\mathbf{nav}_{ref,j}$ is greater than a user-defined threshold c , the two echoes are deemed similar and the data collected during this sequence repetition will be assigned to bin number j . If $corr_{i,j} < c$ for all of the existing reference echoes, a new bin is defined with the new echo as its reference echo. This analysis of the navigator echo occurs in real time and the result is fed back to the running sequence to guide the choice of phase encoding step for the current repetition.

Automatic threshold calibration

The correlation threshold c defines whether two navigator echoes are considered similar enough to contribute to the same bin. The choice of c affects image quality and imaging time. If c is too high, data will be divided among too many k-space bins, and the amount of time required to complete one k-space bin will be unacceptably long. If c is too low, motion correction is compromised. The optimal value of c depends on many factors, including the desired efficiency of the sequence (i.e. what percentage of the acquired data should contribute to the completed k-space) and the choice of navigator slice location and field of view.

We have implemented a method of automatic threshold calibration in which the user specifies a desired efficiency and the appropriate correlation threshold c is dynamically adjusted to meet this efficiency. After 200 sequence repetitions, the reconstruction program determines which bin received the most data frames. The fraction of data frames assigned to

this bin is the current efficiency of the sequence. This efficiency is compared to the user-specified efficiency, and the correlation threshold c is adjusted accordingly to try to make the efficiency of subsequent repetitions match the user specified efficiency. This analysis and adjustment is repeated every 200 sequence repetitions.

Real-time feedback

The real-time navigator analysis and transmission of feedback to the running sequence can be completed in less than 15ms. Analysis of efficiency and adjustment of correlation threshold is also performed during this interval once every 200 acquisitions. This analysis is easily concluded in the same time frame as the real-time analysis of the navigator echo, and does not cause any pause or disruption of the steady state behavior of the sequence.

Estimation of T2* from multi-echo GRE images

T2* maps are calculated pixel by pixel by solving for parameters A and T2* which minimize the root-mean-squared (rms) error for each pixel,

$$err_{rms} = \sqrt{\sum_n \left(S_n - A e^{-TE_n/T_2^*} \right)^2}$$

where S_n is the signal at a given pixel for the n^{th} echo and TE_n is the n^{th} echo time. This solution is achieved by nonlinear curve fitting in Matlab.

Implementation

The FB-BOLD sequence was implemented on a Siemens 3.0 Tesla Trio system, with a custom pulse sequence program and a custom image reconstruction program integrated into the scanner's on-line image reconstruction framework. We used the sequence (Figure 1) for 2D renal BOLD imaging with a single-slice acquisition in an oblique coronal plane in order to compare to the existing 2D BH-BOLD method. Typical sequence parameters are given below. All human scans were performed with IRB approval in a HIPAA compliant manner after informed consent.

Comparison of performance of conventional breath hold vs. prospectively navigated free breathing renal BOLD sequence for single-slice 2D BOLD.

A pilot study of 10 healthy volunteers (all male, age range 19–43, average age 29, no history of kidney disease) was performed. Each subject underwent conventional BH-BOLD with a single coronal image obtained through the largest cross-section of the kidneys, and FB-BOLD with identical sequence parameters but longer imaging time to allow four signal averages. Sequence parameters for this study included GRE acquisition, matrix size 256×256 over a 360×360mm field of view (FOV), 8mm slice thickness, 300 Hz pixel bandwidth, TE = 5, 10, 15, 20, 25, 30, 35, and 40 msec, FA = 25 degrees, fat saturation, and 1 signal average for BH-BOLD and 4 signal averages for FB-BOLD. BH-BOLD TR was 58 msec while the FB-BOLD TR was 95 msec, reflecting the extra time necessary for navigation and real-time sequence feedback. Total BH-BOLD imaging time was 15 sec compared to about 3:00 minutes for FB-BOLD. Efficiency of the FB-BOLD sequence was

user-specified at 60%, and typically about 50–60% was actually achieved (i.e. 50–60% of the collected data was used in the final images).

Image Analysis

For SNR and estimation error comparison, the right and left kidneys were manually segmented on the first echo image and average signal level in the kidney was measured. Noise standard deviation was measured by defining a region of interest (ROI) in the air next to the subject and calculating the standard deviation δ of the Rayleigh distribution from the sample mean $\bar{m}$ according to

$$\delta = \bar{m} \sqrt{\frac{2}{\pi}} \quad (1.1)$$

For $\text{SNR} \gg 1$, δ^2 is a good approximation of the variance of the Rician distribution which characterizes noise in MR images. SNR was defined as the ratio of average signal intensity over the kidney divided by the noise standard deviation δ .

The residual error of T_2^* estimation was calculated as the sum of the squared difference between the estimated T_2^* relaxation curve and the actual multi-echo data points. This calculation was performed over the same manually segmented whole-kidney ROI used for SNR measurement for both right and left kidneys.

Cortical T_2^* was quantified in a manually drawn representative cortical ROI in the right kidney of each subject on both the BH-BOLD and FB-BOLD acquisitions and compared.

Results

The prospectively navigated free-breathing sequence was compared to a conventional breath hold sequence in 10 healthy volunteers. Figure 2 shows typical T_2^* maps resulting from renal BOLD experiments in a healthy volunteer using FB-BOLD with four signal averages (total imaging time about 3:00) compared to single breath hold BH-BOLD (total imaging time 0:15).

SNR of the first echo images was compared, with results shown in Figure 3. The FB-BOLD sequence gives consistently better SNR than the BH-BOLD sequence, as expected given the four signal averages acquired with the FB-BOLD sequence. This demonstrates the flexible tradeoff between imaging time and SNR that is possible with the FB-BOLD sequence.

The mean error of estimation of T_2^* for the FB-BOLD and BH-BOLD sequences is shown in Figure 4. Figure 4 shows that the mean error of estimation was consistently less for the FB-BOLD sequence than BH-BOLD for the right kidney, but consistently higher for the left kidney.

Measurement of T_2^* over a manually drawn cortical ROI in the right kidney of each subject shows an average mean T_2^* value of 55.7 msec for the BH-BOLD data with average

standard deviation of 7.9 msec, compared to an average mean $T2^*$ value of 49.6 msec with FB-BOLD, with average standard deviation of 5.4.

Discussion

The results of the study of 10 subjects show the feasibility of free-breathing BOLD acquisition with real-time navigation that allows for increased SNR with longer imaging times, without the usual limitations related to breath-hold acquisitions. FB-BOLD gave less error in the $T2^*$ fit of the right kidney than BH-BOLD, but showed more error in the $T2^*$ fit of the left kidney.

Advantages of free breathing

While signal averaging could be performed with conventional BH-BOLD imaging averaged across different breath holds to improve SNR, the free breathing FB-BOLD sequence has several advantages over this approach. The position of the kidneys may be inconsistent between breath holds, especially if the subject is short of breath or unaccustomed to breath holding. To avoid shortness of breath, relatively long recovery periods equal to or greater than the breath hold duration are necessary between breath holds. Additionally, breath-holding may cause changes in physiology that influence the measurement of renal BOLD. With the FB-BOLD sequence, the subject breathes naturally. We typically achieve efficiency of about 60%, which makes the FB-BOLD sequence more time efficient than multiple breath holds with interleaved recovery periods.

Mean error of estimation of $T2^*$

Mean error of estimation is decreased in the right kidney with the FB-BOLD sequence but increased in the left kidney compared to BH-BOLD. At the same time, SNR was improved in both kidneys with the FB-BOLD sequence. This interesting result probably reflects the fact that the navigator for the FB-BOLD sequence was placed across the right hemidiaphragm. The poor estimation error in the left kidney with the FB-BOLD sequence suggests that motion of the left kidney is poorly correlated with motion of the right hemidiaphragm. This observation has significance for conventional respiratory gated abdominal imaging, in which a navigator slice is typically placed over the right hemidiaphragm. We have experimented with a refinement of the current FB-BOLD sequence which utilizes volume-selective 2D excitation of a single kidney (28). Such an approach could be used in an interleaved fashion to perform full 3D BOLD imaging of both kidneys, with separate navigators for right and left kidneys which can be placed on the kidneys themselves. Given the results of the current study, we expect that such a method of interleaved single-kidney imaging will result in reduced error of $T2^*$ estimation in both right and left kidneys. This is a topic for future research. We note that error of $T2^*$ estimation must be interpreted with caution, since local B_0 inhomogeneity can cause the actual signal decay to deviate significantly from an ideal exponential (29), in which case improved data quality could actually cause greater error of estimation.

Importance of SNR in renal BOLD MRI

Increased SNR means less corruption of image data with noise, leading to more accurate estimation of $T2^*$. SNR can be traded for increased image resolution, which also improves $T2^*$ estimation by decreasing the contribution of local field inhomogeneity to $T2^*$ (28). Ideally, renal BOLD would be performed with the highest SNR and highest resolution possible. With current renal BH-BOLD sequences, image resolution is limited by low SNR and by the time constraints of breath holding. The new FB-BOLD method addresses this limitation by extending the imaging time beyond a breath hold. For this study, image resolution was the same with BH-BOLD and FB-BOLD to allow direct comparison of the methods. In practice, the increased SNR provided by the FB-BOLD sequence may be traded to some extent for higher image resolution. The optimal tradeoff of SNR vs. image resolution for most accurate $T2^*$ estimation is not obvious and may be the subject of future investigation.

Comparison to previous work

Other sequences using real-time feedback based on navigator echoes have been implemented to reduce motion artifacts. Some sequences use real-time navigator analysis to accept or reject data frames based on motion relative to a single reference navigator (30–33), or to progressively replace previously acquired data frames with frames whose navigators more closely resemble a reference navigator (34). A full 2D image has been used as a navigator to detect motion between echo planar acquisitions in diffusion weighted imaging with real-time feedback to reacquire motion corrupted acquisitions (35). Real-time navigation has also been used to guide optimal ordering of phase encoding steps in a single image k-space to minimize motion artifact (36,37). An approach similar to ours in which all data is kept but is sorted into separate k-space bins based on the navigator has been applied to cardiac imaging (38,39). Prospective navigation with real-time feedback has not been previously applied to abdominal imaging or specifically to imaging of the kidneys.

Scan efficiency

In our experience, a few moments spent coaching the subject before the start of a prospectively navigated scan can result in greatly improved scan efficiency. We instruct subjects to try to slightly extend the time between breaths during which they are completely still, without altering their breathing enough to become short of breath. This simple instruction leads to scan efficiencies of about 60%.

Implications of longer TR requirement of FB-BOLD sequence compared to BH-BOLD

At first glance, the time required to acquire and process a navigator echo and provide real-time feedback to the running sequence seems like a disadvantage of the FB-BOLD sequence, since without this time overhead the TR could be shortened and more signal averages could be obtained in the same overall imaging time. In fact, as discussed in more detail in the Appendix, this lengthening of TR has almost no effect on the SNR efficiency of the sequence.

Limitations

In this study we have not attempted extensive analysis of baseline T2* values in our normal volunteers or studied T2* response to diuretics, nor have we performed reproducibility experiments. Renal BOLD data may be affected by subject variables such as state of hydration, protein intake, or time of day. We did not control for any of these factors, but compared the SNR and T2* fitting error within each subject so that these factors equally affect both methods. We have tested the FB-BOLD sequence in normal volunteers who breathe normally with a rate of 7 to 18 breaths per minute. The performance of FB-BOLD may be adversely affected by rapid or irregular breathing. Conventional respiratory gated scans are sometimes combined with additional motion reduction methods such as PROPELLER (40). We have not incorporated additional motion correction into our FB-BOLD sequence. This may be a direction for future work.

Conclusion:

We have applied prospective navigation with real-time feedback to a multiple echo GRE sequence to allow renal BOLD imaging with free breathing (FB-BOLD). The ability to increase the FB-BOLD scan time far beyond the time of a single breath hold gives renal BOLD images with SNR superior to conventional breath hold BOLD (BH-BOLD) images. In a comparison of 10 subjects imaged with both FB-BOLD and BH-BOLD, the FB-BOLD sequence gives consistently higher SNR in both kidneys and improved error of T2* estimation in the right kidney. Error of T2* estimation in the left kidney is higher with FB-BOLD than conventional BH-BOLD, suggesting that navigation on the right hemidiaphragm does not adequately capture motion of the left kidney with respiration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

3D	three dimensional
BH-BOLD	breath hold BOLD
BOLD	blood oxygen level dependent
CKD	chronic kidney disease
ESRD	end-stage renal disease
FB-BOLD	free-breathing (navigated) BOLD
HIPAA	Health Insurance Portability and Accountability Act
MRI	magnetic resonance imaging

ROI	region of interest
SNR	signal to noise ratio
TR	sequence repetition time

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Figure 1: Pulse sequence diagram for the prospectively navigated FB-BOLD sequence.

The navigator echo is acquired at the beginning of the sequence repetition and is analyzed in real time, with feedback given to the sequence to choose the appropriate phase encoding step for the current “bin” (phase of the respiratory cycle).

Figure 2: Comparison of conventional breath hold (BH-BOLD) and free-breathing (FB-BOLD) sequences.

Representative $T2^*$ maps from one subject are shown with the FB-BOLD sequence (left, 4 signal averages, image time 3:00) and conventional BH-BOLD (right, no signal averaging, image time 0:15). Details of sequence parameters are given in the text.

Figure 3: SNR comparison of FB-BOLD and BH-BOLD.

SNR of the first-echo image was averaged over the kidney. FB-BOLD gives uniformly higher SNR than conventional BH-BOLD, reflecting the expected effect of longer imaging time.

Figure 4: Error of fit for T2* imaging, FB-BOLD compared to BH-BOLD.

The error of T2* fitting is reduced in the right kidney with FB-BOLD compared to conventional BH-BOLD, but increased in the left kidney. One outlying data point was omitted. Units are arbitrary but equal between the x and y axes.