Peer-reviewed version available at Diagnostics 2018, 8, 43; doi:10.3390/diagnostics8030043

Article

Evaluation of Imaging Schemes for Pulsed Arterial Spin Labelling of the Human Kidney Cortex

*Charlotte E. Buchanan[1], Eleanor F. Cox[1], Susan T. Francis[1]**

[1]Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, Nottingham, UK.

charlotte.buchanan@nottingham.ac.uk; eleanor.cox@nottingham.ac.uk; susan.francis@nottingham.ac.uk;

*Correspondence: susan.francis@nottingham.ac.uk

Abstract:

Purpose

A number of imaging readout schemes have been proposed for renal arterial spin labelling (ASL) to quantify kidney cortex perfusion, including gradient echo based methods of balanced fast field echo (bFFE) and gradient-echo echo-planar imaging (GE-EPI), or spin echo based schemes of spin-echo echo planar imaging (SE-EPI) and turbo spin-echo (TSE). Here, we compare these imaging schemes to evaluate the optimal imaging scheme for pulsed ASL (PASL) assessment of human kidney cortex perfusion at 3 T.

Methods

Ten healthy volunteers with normal renal function were scanned using each 2D multislice imaging scheme, in combination with a respiratory triggered FAIR (flow-sensitive alternating inversion recovery) ASL scheme on a 3T Philips Achieva scanner. All volunteers returned for a second identical scan session within two weeks of the first scan session. Comparisons were made between the imaging schemes in terms of perfusion weighted image (PWI) signal-to-noise ratio (SNR) and perfusion quantification, temporal SNR (tSNR), spatial coverage, and repeatability.

Results:

For each imaging scheme, renal cortex perfusion was calculated (bFFE: 276 ± 29 ml/100g/min, GE-EPI: 222 ± 18 ml/100g/min, SE-EPI: 201 ± 36 ml/100g/min, TSE: 200 ± 20 ml/100g/min). Perfusion was found to be higher for GE based readouts compared to SE

based readouts, with significantly higher measured perfusion for the bFFE readout compared to all other schemes ($P < 0.05$), attributed to the greater vascular signal present. Despite the PWI-SNR being significantly lower for SE-EPI compared to all other schemes ($P < 0.05$), the SE-EPI readout gave the highest tSNR and was found to be the most reproducible scheme for the assessment of kidney cortex, with a CoV of 17.2%, whilst minimizing variability of the perfusion weighted signal across slices for whole kidney perfusion assessment.

Conclusion

For the assessment of kidney cortex perfusion, SE-EPI provides optimal tSNR, minimal variability across slices and repeatable data acquired in a short scan time with low specific absorption rate.

Keywords: Magnetic Resonance Imaging, Arterial Spin Labelling, Renal MRI, Perfusion, Renal ASL.

1. Introduction

In clinical practice, renal function is typically determined via serum creatinine measurements to estimate glomerular filtration rate (GFR), however this method is not highly sensitive and changes in GFR may develop relatively late in the progression of Chronic Kidney Disease (CKD). Renal perfusion informs on the delivery of nutrients and oxygen to the tissue and is a key measure by which to monitor renal function. A method to provide reliable and repeatable perfusion assessment of the kidney, in conjunction with precise morphological information, would significantly improve the assessment and monitoring of renal health. Arterial spin labelling (ASL) is a Magnetic Resonance Imaging (MRI) technique that allows the non-invasive quantitative assessment of tissue perfusion, with the advantage that it does not require any exogenous contrast agent, instead using the magnetisation of endogenous labelled blood to provide contrast.

Peer-reviewed version available at Diagnostics 2018, 8, 43; doi:10.3390/diagnostics8030043

The majority of renal ASL studies in the literature have employed a Pulsed ASL (PASL) technique using the flow-sensitive alternating inversion recovery (FAIR) scheme [1–9]. In the FAIR scheme, two images are collected, a selective image which contains non-inverted arterial blood and a non-selective image in which inflowing blood has been magnetically inverted. By subtracting the non-selective image from the selective image a perfusion weighted image (PWI) is formed, which with the appropriate modelling can be quantified to a perfusion map in units of ml/100g/min.

A number of different two-dimensional (2D) imaging readout schemes have been implemented in the literature for renal ASL studies. To determine the optimal readout for renal ASL, a number of factors must be considered. The optimal readout should have a short echo time (TE) in order to provide the highest image signal-to-noise ratio (SNR) and reduce the amount of signal dephasing and distortion. The short intrinsic T_2 and T_2* in the abdomen leads to rapid signal dropout and loss of perfusion signal at longer TEs. The ideal readout should be collected in a short shot length to enable multiple slices through the kidney to be acquired prior to the recovery of the ASL signal, thus enabling whole kidney perfusion assessment. Further, if the acquisition is respiratory triggered, it is important to acquire all images within a respiratory cycle, and ideally within the flat component of the respiratory cycle at end expiration where motion is minimum. Finally, the ideal readout should have a low specific absorption rate (SAR) so that a short temporal spacing between the 2D images can be achieved when collecting a multi-slice dataset.

Echo planar imaging (EPI) is one of the most commonly used readout techniques for ASL of the brain due to its relatively short acquisition time making whole head coverage feasible [10–17]. However, in the body, the larger field-of-view (FOV) means EPI readouts typically have a longer TE (> 10 ms, dependent on parallel imaging acceleration factor) and for high spatial resolution images the acquisition time can become very long resulting in poor image quality, due to susceptibility induced signal inhomogeneities, particularly close to geometrically irregular tissue-air boundaries. Either gradient echo (GE) or spin-echo (SE) based EPI can be used. GE-EPI is more influenced by any B_0 field homogeneity than SE-EPI, since phase shifts from field inhomogeneities, static tissue susceptibility gradients and

chemical shifts are not cancelled. Since EPI has a short acquisition time, of the order of 30 ms, multiple slices at the peak of the ASL signal curve can be imaged, thus low variance is expected in the perfusion weighted ASL signal across a multi-slice dataset. Sokolska *et al*. used a GE-EPI readout combined with pseudo-continuous ASL (pCASL) labelling to assess the feasibility and within subject repeatability of renal perfusion measures [9], whilst Gardener *et al*. employed a SE-EPI readout to acquire multiple slices across the kidney and assessed different breathing strategies to overcome respiratory motion [4].

A balanced fast field echo scheme (bFFE) has been widely used as the image readout for renal ASL [3,5,6,18]. It has the advantage of providing a very short TE and high image SNR. However, the shot length of a bFFE scheme is long, at approximately 300 ms for a typical abdominal FOV with 3 mm voxel resolution. Thus for a multi-slice acquisition, not all slices are collected at the peak of the ASL signal curve, potentially resulting in greater variance in the image perfusion weighted signal across slices in comparison to EPI. In addition, the long shot length limits the number of slices which can be collected when respiratory triggering the data acquisition. bFFE schemes are also limited by their sensitivity to field homogeneity, with banding artifacts apparent in areas of off-resonance in the image. Gillis *et al*. measured inter-study reproducibility of ASL at 3T using a FAIR scheme combined with bFFE readout, and concluded that this provides a repeatable method of measuring renal perfusion [5].

Turbo spin echo (TSE) imaging, also known as fast spin echo (FSE) imaging, is another alternative spin-echo based 2D imaging scheme. Here, the time saved by scanning multiple lines of k-space at once means it is possible to lengthen the TR which allows more time for T_1 recovery, resulting in improved image SNR. A higher number of phase encoding steps can also be used for improved spatial resolution, and susceptibility induced signal losses are low. However, the TE of a TSE readout is typically 50 ms, so some blurring of the image will occur due to T_2 decay, whilst the shot length is long at approximately 160 ms, resulting in slices being acquired at different points in the ASL signal curve and respiratory cycle, and therefore potentially increasing the variance in the perfusion weighted signal across slices. A further limitation of the TSE scheme is the high SAR due to the multiple refocussing pulses

which can result in a long temporal spacing between multi-slice images to keep within SAR limits.

To date, there have been no direct comparisons of these 2D imaging readout schemes for ASL in the kidney. In this work we compare GE-EPI, SE-EPI, bFFE and TSE readout schemes used in combination with a FAIR labelling scheme to assess the optimal scheme(s) for renal ASL.

2. Materials and Methods

Subjects

The study was approved by the local ethics committee and all participants gave informed, written consent. Ten healthy volunteers (age 27 ± 10 years, 5 female) were scanned for approximately one hour on a 3T Philips Achieva MRI scanner using dual-transmit and a 16-channel XLTorso receive coil. To assess the repeatability of each readout scheme, volunteers returned for a second visit, which comprised an identical scan session within 2 weeks of visit 1 scan session. The MRI was performed at the same time of day on all subjects to minimize potential diurnal variations in renal physiologic function. Subjects fasted the previous evening from 8 pm to enable a controlled hydration status for all subjects. To ensure that all volunteers had normal kidney function, blood and urine samples were collected and evaluated by a clinician. Urea, electrolytes and urine protein creatinine ratio were assessed.

MR Acquisition

Initially, balanced turbo field echo (bTFE) localiser scans were acquired in three orthogonal planes to plan placement of the imaging and ASL labelling slabs relative to the kidneys and vessels. The FAIR labelling scheme used a Frequency Offset Corrected Inversion (FOCI) inversion pulse to achieve a 45 mm selective (S) inversion slab (10 mm wider than the imaging volume) and a 400 mm non-selective (NS) inversion slab. Coronal-oblique imaging slices were collected through the kidneys in descending order (lateral – medial) whilst taking care that the selective inversion slab avoided the aorta (Figure 1). Identical readout geometry was acquired on each subject for all imaging schemes, with a 288 x 288 mm FOV, in-plane spatial resolution of 3 mm and 5 mm slice thickness. All readout schemes were acquired with parallel acceleration with a SENSE factor of 2, thus reducing the achievable GE-EPI and SE-

EPI TE, and minimising the readout duration thereby limiting susceptibility related distortions and signal drop out and allowing multiple slices to be acquired to sample the peak of the ASL signal curve.

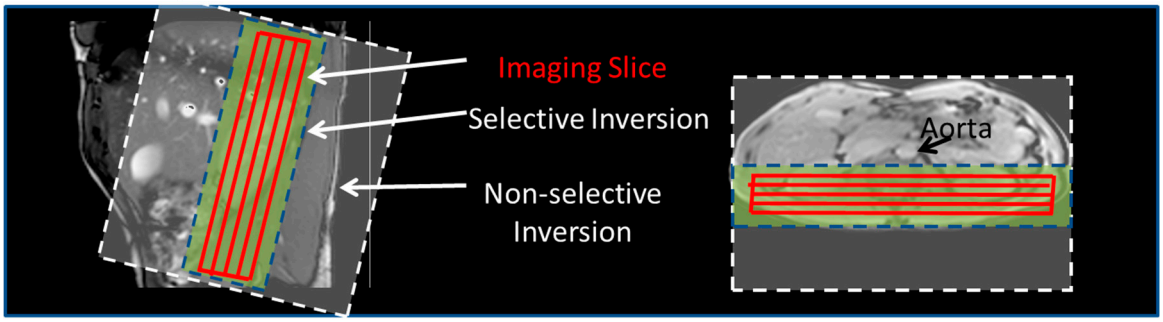

Figure 1. FAIR scheme. Positioning of the selective and non-selective labelling slabs shown relative to the imaging volume of the kidneys, and the aorta.

To suppress any static tissue signal in the perfusion weighted images, in-plane WET (Water suppression Enhanced through T_1 effects) presaturation pulses were applied immediately prior to each S/NS pulse and a sinc post-saturation pulse was applied immediately after. A post label delay (PLD), defined to be the time to centre k-space of the first slice, of 1300 ms was used for bFFE and TSE readouts and 1800 ms for GE-EPI and SE-EPI readouts. This accounted for the different readout duration of each of the schemes (see Table 1), ensuring the maximum perfusion weighted signal was sampled for each scheme. All data sets were acquired respiratory triggered on the S/NS RF pulse, with a minimum repetition time (TR) of 3 s between each S/NS RF pulse. In total, 25 S/NS image pairs were acquired for each readout scheme.

Readout scheme	**Post label Delay (ms)**	**Echo time (ms)**	**Flip angle (º)**	**No. slices (slice gap (mm))**	**Slice spacing (ms)**
bFFE	1300	1.5	45	5 (0)	280
GE-EPI	1800	8	90	5 (0)	40

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 May 2018 doi:10.20944/preprints201805.0386.v1

Peer-reviewed version available at Diagnostics 2018, 8, 43; doi:10.3390/diagnostics8030043

SE-EPI	1800	18	90	5 (0)	60
TSE	1300	50	90	3 (5)	480

Table 1. Imaging parameters for the bFFE, GE-EPI, SE-EPI and TSE readout schemes. The post label delay (PLD) is defined to be the time to the centre of k-space for the first slice.

Base magnetisation M_0 and T_1 relaxation time images were acquired with geometry matched to the ASL readout to allow perfusion quantification. Base magnetisation M_0 images were acquired at the same point in the respiratory cycle as the ASL data using a trigger delay matched to the ASL PLD time. A modified respiratory-triggered inversion-recovery sequence was implemented to map the T_1 relaxation time in the renal cortex. Images were acquired at multiple inversion times (TI) of 200 ms to 1500 ms in 100 ms steps, but with all TIs collected at the same time in the respiratory cycle as the ASL data by introducing an additional delay (Tv*)* following the respiratory trigger and prior to the inversion pulse. T_1 data was collected with a minimum TR of 8 s to allow full signal recovery using a 400 mm NS inversion slab. For GE-EPI and SE-EPI readouts, the multislice T_1 dataset was acquired in descend order, while for the bFFE and TSE readout schemes, the multislice T_1 dataset was acquired for both ascend and descend ordering to increase the dynamic range of TI values [19].

Quantification of renal cortex perfusion and T_1

Analysis was performed using custom written MATLAB programs (Matlab version 8.1, The MathWorks, Inc., Natick, MA, USA). ASL perfusion weighted (PW) difference images were formed by subtracting the non-selective images from the selective images [20]. PW difference images were inspected for motion, misaligned pairs discarded, and the remaining PW difference images averaged to form an average PW difference image (ΔM) for each slice. These were then normalised to the base M_0 image. T_1 maps were formed by fitting the inversion recovery data to a two parameter model. ΔM, T_1 and base M_0 maps were used to generate a renal perfusion (*f*) map, in units of ml/100g/min, by fitting the data to a kinetic

model [21]. To segment the renal cortex, a histogram of kidney T_1 values was produced and threshold to create a cortex mask. These cortex masks were compared across the readout schemes to ensure approximately the same number of voxels were assessed, the average DICE similarity coefficient between visits was calculated as 0.53 ± 0.13. The mean and standard deviation of perfusion in the renal cortex was calculated for both left and right kidney.

Image Quality Assessment

The following quantitative metrics were computed in the renal cortex to assess the quality of perfusion data for each readout scheme: (i) Perfusion weighted image (PWI) SNR: defined as the mean PW signal divided by the standard deviation in the background noise of the PW image; (ii) Temporal SNR (tSNR) of the perfusion weighted image: defined as the mean PW signal divided by the standard deviation across the 25 ASL pairs; (iii) Variance in the PW signal across slices ($var_{\Delta M}$): defined as the standard deviation in the PW signal across the slices divided by the mean PW signal.

Statistical Analysis

Statistical analysis was performed using SPSS software version 21(IBM©). Quantitative variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) depending on normality, with a Shapiro-Wilk test used to test for normality of the data. In all analyses, $P < 0.05$ was considered statistically significant. To assess differences between readout schemes, a repeated measures ANOVA test was used.

For each readout, between- and within-subject variability of measurements was assessed by the coefficient of variation (bCV, wCV). In addition, the coefficient of variation (CoV) of perfusion (standard deviation divided by the mean) was calculated to assess repeatability between scan sessions.

3. Results

All healthy volunteers were confirmed to have normal kidney function, with eGFR > 60 ml/min/1.73m^2, with creatinine of 76 ± 15 μmol/L and urea of 4.2 ± 1.1 mmol/L.

ASL Image Quality

Base M_0 images for each 2D readout scheme are shown in Figure 2 with good data quality for all readouts, and minimal distortions, even for EPI acquisitions. Note that the TSE scheme suffers from blurring, whilst vessels appear brighter in the bFFE image.

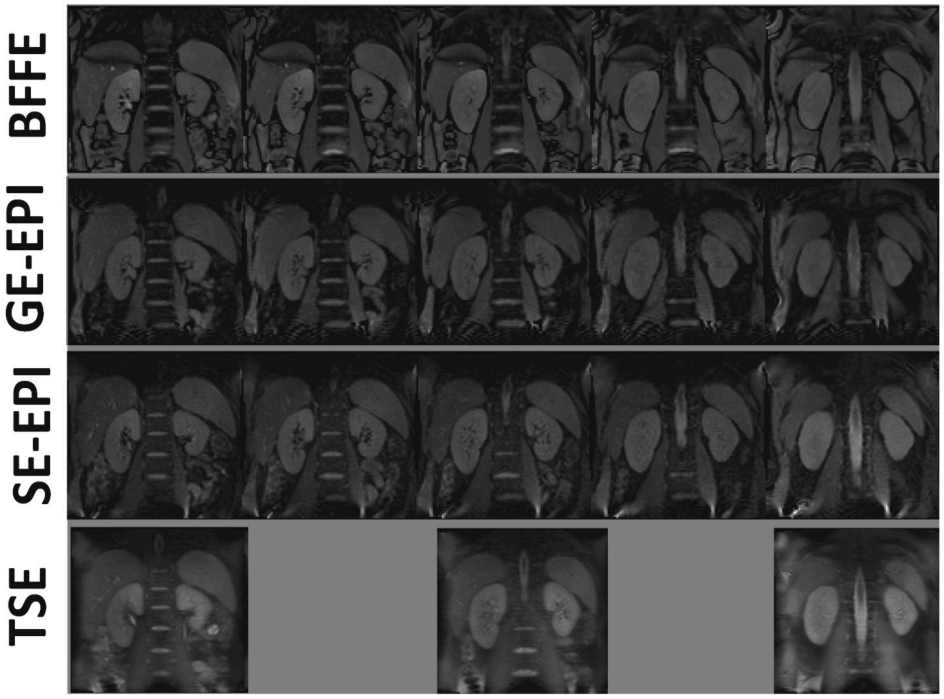

Figure 2. *Example base magnetisation M_0 images for each of readout scheme.*

The TSE ASL scheme had the highest SAR at approximately 70 % of whole body averaged SAR, whilst the SE-EPI, GE-EPI and bFFE ASL schemes all had SAR of less than 35 %. To minimize SAR, the TSE scheme implements a longer temporal spacing between slice acquisitions (see Table 1), limiting the TSE acquisition to three slices acquired at the peak of the ASL signal curve.

Figure 3 shows multi-slice average perfusion weighted images for each readout scheme. The tSNR, PWI-SNR and variability of the perfusion weighted signal ($var_{\Delta M}$) are provided in Table 2. The TSE scheme had the highest PWI-SNR, whilst the SE-EPI had the lowest PWI-SNR. However, tSNR was optimal for the SE-EPI scheme whilst the GE-EPI scheme had the lowest t-SNR. The variability of the perfusion weighted signal across slices ($var_{\Delta M}$) was

Peer-reviewed version available at Diagnostics 2018, 8, 43; doi:10.3390/diagnostics8030043

found to be smallest for the SE-EPI scheme, reflecting this to be a good scheme for multi-slice whole kidney assessment, with the highest variability for the bFFE scheme.

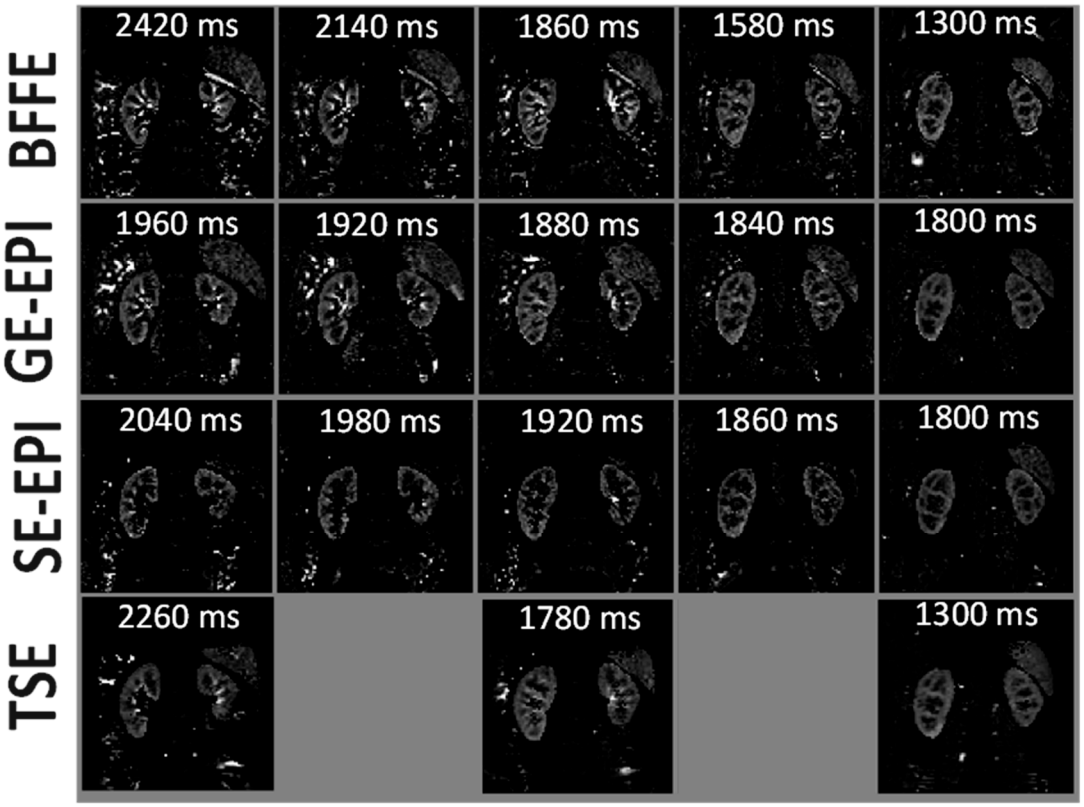

Figure 3. Example perfusion weighted images (PWI) for each scheme (bFFE, GE-EPI, SE-EPI and TSE) from a single subject. The readout time of each slice is indicated on each image.

Readout scheme	**PWI-SNR**	**tSNR**	**$var_{\Delta M}$ (%)**
bFFE	6.2 ± 3.6	2.4 ± 2.0	26 ± 11
GE-EPI	6.3 ± 1.5	1.5 ± 0.8	20 ± 5
SE-EPI	4.9 ± 1.5	2.6 ± 1.6	11 ± 3
TSE	8.5 ± 4.1	2.4 ±1.8	20 ± 4

Table 2: Perfusion weighted image SNR (PWI-SNR), temporal SNR (tSNR) and variability of the perfusion weighted signal ($var_{\Delta M}$) for each scheme.

Perfusion Quantification

Mean renal cortex perfusion across all readout schemes was 223 ± 11 ml/100g/min, the error indicates the standard error of the perfusion values across readout schemes. For each readout scheme, the measured renal cortex perfusion values for visit 1 are shown in Figure 4, and found to be bFFE: 276 ± 29 ml/100g/min, GE-EPI: 222 ± 18 ml/100g/min, SE-EPI: 201 ± 36 ml/100g/min, TSE: 200 ± 20 ml/100g/min. A repeated measures ANOVA showed the bFFE readout produced consistently higher perfusion values compared to the other three schemes ($p = 0.03$), but also had the largest variance between subjects. The SE-EPI scheme gave the lowest intra-subject variance.

The between-subject variation (bCV) of the schemes was 53.3%, 23.7%, 26.2%, 35.9% for bFFE, GE-EPI, SE-EPI and TSE. The within-subject variation (wCV) was 18.8 % for bFFE and 23.9% for GE-EPI, and 15.1% for SE-EPI and 17.2% for TSE.

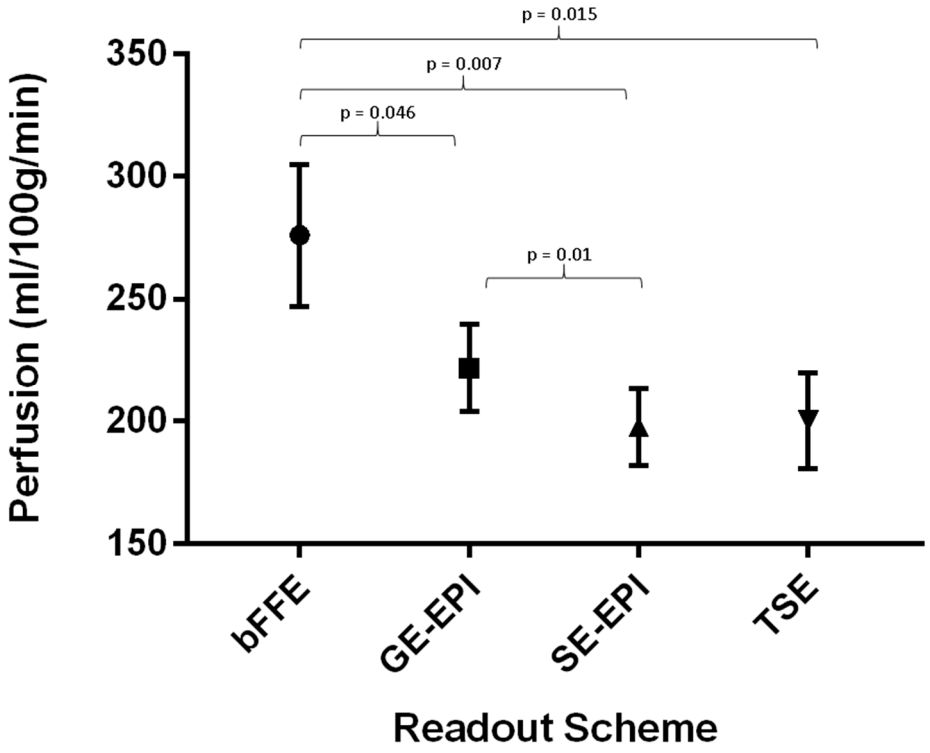

Figure 4. Renal cortical perfusion values measured from each readout scheme for Visit 1. Values shown are the mean perfusion values with error bars showing the standard error on the mean. The bFFE readout gave significantly higher perfusion values than the other

Peer-reviewed version available at Diagnostics 2018, 8, 43; doi:10.3390/diagnostics8030043

readouts (repeated measures ANOVA, p =0.03). A significant difference was observed between SE-EPI and GE-EPI., with p values of post-hoc paired t-tests shown.

Repeatability

The most repeatable readout scheme was SE-EPI, which had a CoV of 17.2%; the least repeatable scheme was the GE-EPI scheme with a CoV of 28.3 %. For each readout scheme, across the 10 subjects there were no significant difference in renal cortex perfusion values between Visit 1 and Visit 2 ($p > 0.05$).

4. Discussion

Previous renal ASL studies have used a variety of readout schemes in combination with FAIR labelling. In this work, a comparison of balanced fast field echo (bFFE), gradient-echo EPI (GE-EPI), spin-echo EPI (SE-EPI) and turbo spin echo (TSE) schemes is made for renal ASL. For all schemes, multi-slice coverage could be achieved with five contiguous slices collected for bFFE, GE-EPI and SE-EPI and three slices with a 5 mm slice gap for TSE, the higher SAR leading to wider readout spacing for the TSE scheme. GE-EPI and SE-EPI could achieve whole kidney coverage in the shortest amount of time.

In this work, the cortical perfusion was higher for gradient-echo schemes (GE-EPI and bFFE) in comparison to spin-echo based schemes (SE-EPI and TSE). Perfusion calculated from bFFE readout data was found to be significantly higher than all other schemes which could be attributed to the presence of vascular signal in these images.

When comparing the SNR, the SE-EPI scheme gave a significantly lower PWI-SNR compared to the other schemes; however this could in part be attributed to the reduction in vascular signal present in the SE-EPI images. This is also supported by the fact that the SE-EPI scheme had the highest temporal SNR, suggesting lowest fluctuations from pulsatile vessels.

The SE-EPI scheme gave the lowest variance in perfusion weighted signal ($var_{\Delta M}$) across slices of all the readout schemes. This is unsurprising as the SE-EPI scheme has a short shot length per slice, and so all slices are acquired at almost the same point on both the ASL signal

curve and in the respiratory cycle, resulting in a small variance in the signal of each slice. Conversely, TSE readouts have a long shot length; this yielded the highest variance in signal across slices.

All 2D readout schemes were determined to be repeatable with a CoV of 28.2% or less. SE-EPI was found to be optimal with a CoV of 17.2%. ASL quantitative measurements of normal perfusion show good within-subject variability and repeatability. These estimates form the basis for interpreting optimal readout schemes for guiding future study design in assessing ASL renal perfusion.

5. Conclusions

FAIR ASL measures have been collected for bFFE, GE-EPI, SE-EPI and TSE readout schemes. All schemes were found to be repeatable with coefficients of variation less than 29% for all techniques. When comparing all four techniques we conclude that SE-EPI provides optimal temporal SNR, consistency across slices, repeatability between sessions and has the lowest specific absorption rate.

Acknowledgments: This work was funded by the Dr Hadwen Trust. The Dr Hadwen Trust (DHT) is the UK's leading non-animal biomedical research charity that exclusively funds and promotes human-relevant research that replaces the use of animals whilst supporting the progress of medicine.

Author Contributions: SF conceived and designed the experiments; CB, SF and EC performed the experiments; CB analyzed the data; CB, EC and SF wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Cutajar, M.; Thomas, D. L.; Hales, P. W.; Banks, T.; Clark, C. a.; Gordon, I. Comparison of ASL and DCE MRI for the non-invasive measurement of renal blood

flow: Quantification and reproducibility. *Eur. Radiol.* **2014**, *24*, 1300–1308, doi:10.1007/s00330-014-3130-0.

2. Dong, J.; Yang, L.; Su, T.; Yang, X.; Chen, B.; Zhang, J.; Wang, X.; Jiang, X. Quantitative assessment of acute kidney injury by noninvasive arterial spin labeling perfusion MRI: a pilot study. *Sci. China. Life Sci.* **2013**, *56*, 745–50, doi:10.1007/s11427-013-4503-3.

3. Gardener, A.; Francis, S. Multi-slice kidney perfusion using SE-EPI FAIR: Optimised acquisition and analysis strategies. In *Proceedings 17th Scientific Meeting, International Society for Magnetic Resonance in Medicine*; 2009; Vol. Honolulu, p. 2035.

4. Gardener, A. G.; Francis, S. T. Multislice perfusion of the kidneys using parallel imaging: Image acquisition and analysis strategies. *Magn. Reson. Med.* **2010**, *63*, 1627–1636, doi:10.1002/mrm.22387.

5. Gillis, K. a; McComb, C.; Foster, J. E.; Taylor, A. H. M.; Patel, R. K.; Morris, S. T. W.; Jardine, A. G.; Schneider, M. P.; Roditi, G. H.; Delles, C.; Mark, P. B. Inter-study reproducibility of arterial spin labelling magnetic resonance imaging for measurement of renal perfusion in healthy volunteers at 3 Tesla. *BMC Nephrol.* **2014**, *15*, 23, doi:10.1186/1471-2369-15-23.

6. Martirosian, P.; Klose, U.; Mader, I.; Schick, F. FAIR True-FISP Perfusion Imaging of the Kidneys. *Magn. Reson. Med.* **2004**, *51*, 353–361, doi:10.1002/mrm.10709.

7. Pedrosa, I.; Rafatzand, K.; Robson, P.; Wagner, A. a.; Atkins, M. B.; Rofsky, N. M.; Alsop, D. C. Arterial spin labeling MR imaging for characterisation of renal masses in patients with impaired renal function: Initial experience. *Eur. Radiol.* **2012**, *22*, 484–492, doi:10.1007/s00330-011-2250-z.

8. Robson, P. M.; Madhuranthakam, A. J.; Dai, W.; Pedrosa, I.; Rofsky, N. M.; Alsop, D. C. Strategies for reducing respiratory motion artifacts in renal perfusion imaging with arterial spin labeling. *Magn. Reson. Med.* **2009**, *61*, 1374–1387,

343 doi:10.1002/mrm.21960.

344 9. Sokolska, M.; Thomas, D.; Bainbridge, A.; Golay, X.; Taylor, S.; Punwani, S.; Pendse,
345 D.; Uk, L. Renal Pseudo-continuous Arterial Spin Labelling (pCASL) MRI : A
346 Repeatability Study . **2014**, 1–13.

347 10. Alsop, D. C.; Detre, J. a.; Golay, X.; Günther, M.; Hendrikse, J.; Hernandez-Garcia,
348 L.; Lu, H.; Macintosh, B. J.; Parkes, L. M.; Smits, M.; van Osch, M. J. P.; Wang, D.
349 J. J.; Wong, E. C.; Zaharchuk, G. Recommended implementation of arterial spin-
350 labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion
351 study group and the european consortium for ASL in dementia. *Magn. Reson. Med.*
352 **2014**, *0*, doi:10.1002/mrm.25197.

353 11. Brookes, M. J.; Morris, P. G.; Gowland, P. A.; Francis, S. T. Noninvasive
354 measurement of arterial cerebral blood volume using Look-Locker EPI and arterial
355 spin labeling. *Magn. Reson. Med.* **2007**, *58*, 41–54, doi:10.1002/mrm.21199.

356 12. Gunther, M.; Bock, M.; Schad, L. R. Arterial spin labeling in combination with a look-
357 locker sampling strategy: Inflow turbo-sampling EPI-FAIR (ITS-FAIR). *Magn.*
358 *Reson. Med.* **2001**, *46*, 974–984, doi:10.1002/mrm.1284.

359 13. Hall, E.; Hall, E.; Wesolowski, R.; Wesolowski, R.; Gowland, P.; Gowland, P.;
360 Francis, S.; Francis, S. Improved detection and estimation of perfusion using high
361 spatial resolution ASL at 7T. In *Proceedings 17th Scientific Meeting, International*
362 *Society for Magnetic Resonance in Medicine, Honolulu*; 2009; p. 1529.

363 14. Kim, S. G. Quantification of relative cerebral blood flow change by flow-sensitive
364 alternating inversion recovery (FAIR) technique: Application to functional mapping.
365 *Magn. Reson. Med.* **1995**, *34*, 293–301, doi:10.1002/mrm.1910340303.

366 15. Wong, E. C. Quantifying CBF with pulsed ASL: Technical and pulse sequence factors.
367 In *Journal of Magnetic Resonance Imaging*; 2005; Vol. 22, pp. 727–731.

368 16. Wong, E. C. An introduction to ASL labeling techniques. *J. Magn. Reson. Imaging*
369 2014, *40*, 1–10.

17. Wong, E. C.; Buxton, R. B.; Frank, L. R. A theoretical and experimental comparison of continuous and pulsed arterial spin labeling techniques for quantitative perfusion imaging. *Magn. Reson. Med.* **1998**, *40*, 348–55.

18. Park, S. H.; Wang, D. J. J.; Duong, T. Q. Balanced steady state free precession for arterial spin labeling MRI: Initial experience for blood flow mapping in human brain, retina, and kidney. *Magn. Reson. Imaging* **2013**, *31*, 1044–1050, doi:10.1016/j.mri.2013.03.024.

19. Hoad, C. L.; Palaniyappan, N.; Kaye, P.; Chernova, Y.; James, M. W.; Costigan, C.; Austin, A.; Marciani, L.; Gowland, P. a.; Guha, I. N.; Francis, S. T.; Aithal, G. P. A study of T<inf>1</inf> relaxation time as a measure of liver fibrosis and the influence of confounding histological factors. *NMR Biomed.* **2015**, *28*, 706–714, doi:10.1002/nbm.3299.

20. Cox, E. F.; Buchanan, C. E.; Bradley, C. R.; Prestwich, B.; Mahmoud, H.; Taal, M.; Selby, N. M.; Francis, S. T. Multiparametric renal magnetic resonance imaging: Validation, interventions, and alterations in chronic kidney disease. *Front. Physiol.* **2017**, *8*, 1–15, doi:10.3389/fphys.2017.00696.

21. Buxton, R. B.; Frank, L. R.; Wong, E. C.; Siewert, B.; Warach, S.; Edelman, R. R. A general kinetic model for quantitative perfusion imaging with arterial spin labeling. *Magn. Reson. Med.* **1998**, *40*, 383–396, doi:10.1002/mrm.1910400308.