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Cerebral blood flow characteristics following hemodialysis initiation in older adults: A prospective longitudinal pilot study using arterial spin labeling imaging

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ABSTRACT

Purpose: To investigate cerebral blood flow (CBF) characteristics before and after hemodialysis initiation and their longitudinal associations with global cognitive function in older adults.

Methods: A cohort of 17 older end-stage renal disease patients anticipating standard thrice-weekly hemodialysis and a group of 11 age- and sex-matched healthy control volunteers were recruited for brain perfusion imaging studies using arterial spin labeling. Hemodialysis patients participated in a prospective longitudinal study using brain magnetic resonance imaging and global cognitive assessment using the Modified Mini-Mental State Examination (3MS) at two time points: baseline, 2.9 ± 0.9 months before, and follow-up, 6.4 ± 2.4 months after hemodialysis initiation. Healthy controls were imaged once using the same protocol. CBF analyses were performed globally in grey and white matter and regionally in the hippocampus and orbitofrontal cortex. Covariate-adjusted linear mixed-effects models were used for statistical analyses (significance: $p < 0.05$; marginal significance: $p < 0.1$).

Results: At baseline, global and regional CBF was significantly higher in hemodialysis patients than in healthy controls. However, after approximately 6 months of hemodialysis, CBF declined substantially in hemodialysis patients, and became comparable to those in healthy controls. Specifically, in the hemodialysis patients, CBF declined non-significantly globally for grey and white matter and significantly regionally in the hippocampus and orbitofrontal cortex. Marginally significant associations were observed between 3MS scores and regional CBF measurements in the hippocampus and orbitofrontal cortex at baseline and follow-up, and between longitudinal changes.

Conclusion: The significant decline in CBF after hemodialysis initiation and the observed association between longitudinal changes in regional CBF and 3MS scores suggest that decreased brain perfusion may contribute to the observed cognitive decline.

Abbreviations: ASL, arterial spin labeling; CBF, cerebral blood flow; CI, cognitive impairment; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MRI, magnetic resonance imaging

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1. Introduction

Chronic kidney disease (CKD) is the ninth leading cause of death in the United States (Chronic Kidney Disease Basics, 2018). CKD can be categorized into five major stages based on measures of kidney function, including estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (United States Renal Data System, 2017). After CKD progresses to end-stage renal disease (ESRD), or kidney failure (stage 5: eGFR $<$ 15 ml/min/1.73 mm^2), renal replacement therapy is required through kidney transplant or dialysis (i.e., hemodialysis or peritoneal dialysis) (United States Renal Data System, 2017).

In the United States, hemodialysis is the dominant renal replacement therapy. Approximately 88% of patients with diagnosed ESRD initiate hemodialysis, and a majority of them are aged older than 55 years (United States Renal Data System, 2017; Rocco, 2015). Up to 70% of older hemodialysis patients have moderate to severe cognitive impairment (CI), a higher prevalence than in matched pre-dialysis CKD and non-CKD populations (Murray et al., 2006; Murray, 2008). A recent study in older ESRD adults also found that the incidence of stroke increases several-fold after hemodialysis initiation (Murray et al., 2013).

Conventional routine hemodialysis may increase the risk of cerebral vascular dysfunction and CI, especially in the elderly, who are more susceptible to cerebral damage due to an aging vasculature. Hemodialysis causes circulatory stress (e.g., acute electrolyte and volume shifts) that can induce significant hemodynamic changes (e.g., blood pressure and flow velocity), transient hypotension and cerebral hypoperfusion, arterial hypoxemia, and frequent cerebral ischemia (Wolfgram et al., 2014; MacEwen et al., 2017; Polinder-Bos et al., 2018; Gottlieb et al., 1987; Hata et al., 1994; Postiglione et al., 1991; Hoshino et al., 2014; Findlay et al., 2019). Although these acute intradialytic changes can normalize after hemodialysis sessions, repeated hemodialysis may result in permanent cerebrovascular dysfunction that can initiate and exacerbate other cerebral structural and functional abnormalities, causing further CI and even hemorrhagic strokes. Permanent cerebrovascular dysfunction is mainly manifested by cerebrovascular endothelial dysfunction and impaired auto-regulation of brain perfusion (Dubin et al., 2011).

Brain perfusion characteristics before hemodialysis initiation and after a period of maintenance hemodialysis can provide valuable information regarding the origins of increased CI prevalence and elevated incidence of stroke in older hemodialysis patients. In the past years, studies have investigated characteristics of cerebral blood flow (CBF) in both non-dialysis and maintenance dialysis ESRD patients using different imaging methods (Zheng et al., 2016a, 2016b; Jiang et al., 2016; Kuwabara et al., 2002; Fazekas et al., 1996; Vorstrup et al., 1992; Hirakata et al., 1992; Mathew et al., 1985; Prohovnik et al., 2007; Cheng et al., 2018). Most of these studies were cross-sectional, with populations of mostly younger individuals (Zheng et al., 2016a, 2016b; Jiang et al., 2016), or groups with large age ranges or unmatched ages between patients and controls (Prohovnik et al., 2007; Kuwabara et al., 2002; Fazekas et al., 1996; Vorstrup et al., 1992; Hirakata et al., 1992). Some studies suggest that compared with controls, hemodialysis patients experienced low CBF (Fazekas et al., 1996; Prohovnik et al., 2007), while other studies found elevated CBF (Zheng et al., 2016a, 2016b; Jiang et al., 2016; Kuwabara et al., 2002; Vorstrup et al., 1992; Hirakata et al., 1992; Mathew et al., 1985). Only two of these studies included both pre-hemodialysis and hemodialysis patients (Jiang et al., 2016; Kuwabara et al., 2002): one study demonstrated widespread regional CBF decline in hemodialysis compared with pre-hemodialysis patients (e.g., frontal cortex) (Jiang et al., 2016), while the other found no significant CBF differences between the two groups (Kuwabara et al., 2002). One perfusion study comparing pre-peritoneal dialysis and peritoneal dialysis patients found higher CBF in the hippocampus in peritoneal dialysis patients, which was related to an observed decline in executive function (Cheng et al., 2018).

Recently, arterial spin labeling (ASL) (Detre et al., 1992), a non-invasive and non-contrast enhanced magnetic resonance imaging (MRI) approach, has been used in several studies to measure brain perfusion in ESRD patients (Jiang et al., 2016; Prohovnik et al., 2007; Cheng et al., 2018). However, none of these studies have accounted for the patient-dependent longitudinal relaxation time (T_1) of blood (T_{1B}), which affects CBF quantification in the presence of anemia; anemia is common in CKD patients and becomes severe in hemodialysis patients (Hsu et al., 2002; Astor et al., 2002; Fishbane and Spinowitz, 2018).

To investigate CBF characteristics before and after hemodialysis initiation, and their longitudinal associations with global cognitive function, we performed a prospective longitudinal brain perfusion pilot study using ASL with a cohort of older ESRD patients. Our major specific hypotheses were: 1) that CBF changes significantly approximately 6 months after hemodialysis initiation, especially in the hippocampus and frontal cortical area (Jiang et al., 2016; Cheng et al., 2018), and 2) that the observed CBF changes are correlated with cognitive declines (Murray et al., 2006; Murray, 2008). In addition, we sought to investigate whether baseline and follow-up CBF measurements from hemodialysis patients are higher than those from a healthy population as found by other studies (Zheng et al., 2016a, 2016b; Jiang et al., 2016; Kuwabara et al., 2002; Vorstrup et al., 1992; Hirakata et al., 1992; Mathew et al., 1985) by performing single-session brain perfusion studies with age- and sex-matched healthy control volunteers.

2. Materials and methods

2.1. Overview of study design

This study consisted of two groups of older participants: a group of ESRD patients who transitioned to standard thrice-weekly hemodialysis (called hemodialysis patients in the following) and a group of age- and sex-matched healthy control volunteers (called controls in the following). Hemodialysis patients participated in a longitudinal study with two sessions: baseline before and follow-up after hemodialysis initiation. Controls underwent a single MRI exam. All participants provided written informed consent to participate, and the study protocol was approved by the University of Minnesota Institutional Review Board.

Previous work reported that studies performed during or immediately after hemodialysis could induce adverse acute effects on brain physiology and cognitive function (Ishida et al., 1999; Gottlieb et al., 1987; Hata et al., 1994; Postiglione et al., 1991; Hoshino et al., 2014; Findlay et al., 2019), which we sought to avoid. In addition, our previous studies suggest that cognitive function varies across a 2-day dialysis cycle (before, during, immediately after, and the day after dialysis), and is worst during dialysis and best before or on the day after dialysis (Murray, 2008). Other studies also found that optimal cognitive function occurs about 24 h after dialysis but worsens at times further out from the last dialysis session (Ratner et al., 1983; Lewis et al., 1980). Thus, for our study, to avoid acute effects of hemodialysis, cognitive function and MRI studies were performed several hours prior to or at least 24 h after a hemodialysis session.

All participants were required to refrain from food or drink containing caffeine for at least 8 h before the MRI exam or cognitive assessment (Cameron et al., 1990). All hemodialysis patients were required to maintain similar diet, fluid intake, and exercise levels across sessions by using a self-reported log established at baseline as a reference. Each MRI or cognitive assessment study for each participant was scheduled at a similar time of day.

2.2. Participant selection

Inclusion criteria for patients were: ability to provide consent, fluency in English, and the ability to complete up to 30 min of cognitive testing and a 1-hour MRI exam. Exclusion criteria for patients were: acute psychiatric illness that would impede cognitive testing; severe CI and inability to complete the Modified Mini-Mental State Examination

(3MS) (Teng and Chui, 1987); active chemical dependency, such as alcohol, narcotics, or other drugs; being legally blind or unable to complete cognitive tests due to visual loss or deafness; having undergone renal transplant at the time of screening or at baseline; and history of severe cardiovascular diseases. Recruitment criteria for controls were: no history of neurological disorders, cardiovascular or renal deficiency or diseases, diabetes, or hypertension; and no active chemical dependency.

2.3. MRI

Studies were performed on a 1.5 T Phillips Ingenia MRI scanner. The study protocol consisted of a scout localizer using gradient recalled echo imaging in three orthogonal orientations (sagittal, oblique coronal, and axial), anatomic T_1-weighted imaging using magnetization prepared rapid acquisition gradient echo with a 0.9 × 0.9 × 1.0 mm^3 resolution, and perfusion imaging using pseudo-continuous arterial spin labeling (PCASL) (Alsop et al., 2015), and other standard clinical imaging scans, including T_2-weigthed FLAIR imaging, diffusion tensor imaging with a b value equal to 1000 s/mm^2, and T_2*-weighted imaging. The major parameters for PCASL imaging using gradient echo planar imaging readout were: TR/TE = 4000/16 ms; flip angle = 90°; FOV = 240 × 240 mm^2; matrix size = 64 × 64; in-plane resolution = 3.75 × 3.75 mm^2; slice thickness/gap/number = 3.75 mm /0.75/33; labeling duration/post-labeling delay = 1.5/1.4 s; and number of label and control images = 80.

2.4. Cognitive assessment and laboratory measures

Global cognitive function was assessed for each hemodialysis patient using the 3MS, a 100-point validated measure of global function used in many population-based studies (Teng and Chui, 1987). Assessment of cognitive function was performed within 1 week before or after MRI examinations by neuropsychologist-trained BRain IN Kidney disease (BRINK) study personnel (Murray et al., 2016). To minimize practice effects, alternate versions of 3MS tests were administered for baseline and follow-up cognitive assessments. To minimize distraction, the cognitive testing was administered in a quiet room. During the visits for cognitive function assessments, blood pressures and a serum hemoglobin were measured as parts of the standard BRINK protocol in the hemodialysis patients.

We also collected medication records if available at both visits; however for most post-dialysis initiation patients, their medication records were kept at the dialysis centers and not accessible to us. Of note, it is standard clinical practice for severe CKD and dialysis patients to monitor anemia with monthly hemoglobin, iron and ferritin levels, and administer erythropoiesis-stimulating agents (ESAs) including human EPO and oral or IV to maintain a hemoglobin in the 10.0–11.5 mg/dL range (Kidney Disease, 2012). According to the United States Renal Data Services (USRDS) 2018 annual data report (United States Renal Data System, 2018), for 2015–2016, 78% of US hemodialysis patients were on a monthly ESA and approximately 61% were on monthly IV iron. Thus for the purposes of this study we would expect that the majority of the hemodialysis patients at follow- up would have been on ESAs and iron treatment during the prior year.

2.5. Data analysis

2.5.1. Image processing tools and region of interest (ROI) definitions

Image processing operations, such as motion correction, co-registration and segmentation, were performed with SPM8 (Functional Imaging Laboratory, University College London, London, UK). In addition to global grey matter (GM) and white matter (WM) CBF, CBF in brain regions (e.g., the hippocampus and orbitofrontal cortex) (Jiang et al., 2016; Cheng et al., 2018) associated with previously observed cognitive impairment (e.g., deficiency in memory and executive function) (Murray et al., 2006; Murray, 2008) was specifically investigated. The ROIs for GM and WM were defined using a threshold of 0.75 for the tissue type probability maps from the segmentation of high-resolution T_1-weighted anatomic images that had been co-registered to the ASL series. The hippocampus was segmented using FIRST (FMRIB's Integrated Registration and Segmentation Tool) (Patenaude et al., 2011) tool within the FSL package (FMRIB Centre, University of Oxford, Oxford, UK). The ROI for orbitofrontal cortex was achieved by inverse transformation of the corresponding ROI in the Harvard-Oxford cortical and subcortical structural atlas template (Desikan et al., 2006) into the ASL image space. ROI-based CBF analyses were performed using in-house scripts implemented within Matlab 8.6 (MathWorks, Natick, MA, USA).

2.5.2. ASL image Pre-Processing

Each ASL image series was first evaluated for subject motion. Whenever the translational motion was larger than 1 mm or the rotation around any axis was more than 1°, motion correction was performed using tri-linear interpolation with the mean image of the ASL series as the reference. In addition, when motions for a pair of labeling and control images were larger than 2 mm in translation or 2° in rotation around any axis, this pair of images was excluded from further processing or analysis. The mean image of the ASL series was used as the reference for the co-registration between anatomic images and ASL CBF map. After motion correction, each ASL label-control image series was pairwise subtracted to generate a perfusion-weighted imaging series. Each perfusion-weighted imaging series was further averaged to produce a mean perfusion-weighted image. The mean perfusion-weighted image was then used in CBF quantification.

2.5.3. CBF quantification

CBF quantification employed the recommended single-blood compartment model (Alsop et al., 2015) with T_{1B} values that were estimated based on a participants' hemoglobin levels and the previously proposed general T_{1B} model (Hales et al., 2016). For hemodialysis patients, hemoglobin levels were derived from blood samples obtained during baseline and follow-up visits; for each control, an age- and sex-dependent hemoglobin level was applied (Mahlknecht and Kaiser, 2010). Since arterial blood oxygen saturation level has minimal effects on T_{1B} (Hales et al., 2016), a fixed normal arterial blood oxygen saturation level, 0.97, was used to estimate T_{1B} for all participants.

2.5.4. ROI-based analysis

To avoid signal intensity modulation and extensive non-linear interpolation of the quantitative perfusion data, all CBF analyses were performed in the ASL image space. Therefore, for each participant, the high-resolution anatomic images along with associated ROIs were co-registered to the mean image of the ASL series. As the ASL data were lower resolution than the anatomic data, down-sampling of the anatomic data resulted in some of the ROIs extending beyond the desired targeted regions. To ensure that the mean CBF estimates were from the tissue of interest, the co-registered ROIs were further conservatively limited to exclude voxels of ROI masks outside of the targeted regions with the help of visual inspection. To further reduce the impact of subtraction errors resulting from residual physiologic motion and potential intravascular perfusion signals, trimmed mean signals within ROIs were used as the final perfusion measurements by excluding the 5% of voxels with the lowest and highest values (Li and Metzger, 2013; Li et al., 2013).

We compared CBF measurements between left and right hippocampi for each group, and found no significant differences between bilateral regions. Therefore, an overall mean CBF within a single ROI covering both hippocampal regions was obtained for each participant and used for statistical analyses.

2.6. Statistical analysis

Statistical analyses were performed using R version 3.5.1 (Core Team, 2016). Comparisons of different measures between groups or across time and evaluation of associations among these measures and their changes were achieved using linear mixed effects models with - adjustments for age and sex, and for other biological covariates, such as baseline eGFR, diabetes status and blood pressures. For any performed analysis, statistical significance was defined as a p value less than 0.05, and marginal significance as a p value less than 0.1.

3. Results

An initial group of 17 ESRD patients were recruited from the BRINK study cohort (Murray et al., 2016). All hemodialysis patients successfully completed two cognition assessment sessions at baseline and at 6-month follow-up, but only 14 completed both MRI sessions. In addition, the data from one patient were excluded due to poor data quality resulting from excessive motion during the MRI exam. Therefore, a total of 13 hemodialysis patients were included for the final data analysis. A total of 11 age- and sex-matched controls were recruited from nearby communities. The baseline and follow-up assessments in the hemodialysis patients occurred 2.9 ± 0.9 months before and 6.4 ± 2.4 months after hemodialysis initiation, respectively. Table 1 describes the demographic and characteristics of the study groups.

Mean age of the hemodialysis patients was 64 years, and there were no significant differences in age or sex distribution between the hemodialysis (n = 13) and control (n = 11) groups (p = 0.438). The mean 3MS score of 93 ± 6 indicates normal baseline cognitive function in the hemodialysis cohort for a mean education level of 14 years. For the (13/14) patients for whom we have medication data at baseline, two were on anemia treatment with an ESA and two on iron treatment. At the follow-up dialysis visit, data for ESA and iron medications administered at the dialysis center were not available (proprietary data of the dialysis centers).

No significant hemoglobin level differences were found between baseline and 6-month follow-up for hemodialysis patients (p = 0.273) (Table 1), but hemoglobin levels were significantly associated with age and sex, with p values of 0.002 and 0.049, respectively. In addition, at follow-up, four patients became non-hypertensive with observed significant decrease of systolic blood pressure (p = 0.003), and one patient has reported hear failure (Table 1).

Analyses of longitudinal changes in 3MS showed that hemodialysis patients experienced a significant decline in global cognitive function approximately 6 months after hemodialysis initiation (Fig. 1), from a score of 93 ± 6 to 90 ± 8, consistent with declining from normal cognitive function to early mild CI.

Global GM and WM CBF measurements from hemodialysis and control groups are presented in Fig. 2. At baseline, global CBF within GM and WM was significantly higher in hemodialysis patients than in healthy controls. After 6 months of hemodialysis, these differences attenuated and became non-significant. This is because CBF declined in both GM and WM in the hemodialysis patients, although non-significantly. No significant associations were observed between global CBF in GM and WM and the 3MS score at baseline or at follow-up. Similarly, we compared regional CBF in the hippocampus and orbitofrontal cortex between the hemodialysis and control groups (Fig. 3). Regional CBF was significantly higher in hemodialysis patients than in healthy controls at baseline, decreased significantly after 6 months of hemodialysis (vs. non-significantly globally), and became comparable to those of healthy controls at follow-up. Correlation analyses revealed marginally significant associations between 3MS scores and CBF measurements in the hippocampus and orbitofrontal cortex at both baseline and follow-up (Fig. 4).

Statistical analyses were also performed to evaluate the associations between longitudinal changes in CBF and 3MS score. Longitudinal percentage changes of CBF measurements in GM, WM, the hippocampus and orbitofrontal cortex, and those of 3MS scores are shown in Fig. 5. No associations were found between longitudinal changes in global CBF within GM and WM, and those in 3MS scores, but marginally significant associations were observed between longitudinal changes in regional CBF in the hippocampus and orbitofrontal cortex and those in 3MS scores (Fig. 6).

Our analyses indicated that the time interval between baseline and follow-up studies, blood pressure and hemoglobin level, as well as the status of diabetes and heart failure, had no impact on the observed either global or regional CBF changes.

Table 1
Demographic and characteristics of end-stage renal disease patients and control volunteers. *

Variable	Patients (n = 13)	Controls (n = 11)
Age (years)	64 ± 9	66 ± 7
Gender (M/F)	7/6	6/5
Education (years)	14 ± 3	–
eGFR (mL/min per 1.73 m^2)	10.8 ± 4.3	–
Diabetes	5/13	0/11
Hypertension		
	13/13	0/11
Baseline -		
	9/13	
Follow-up		
Blood Pressure (mm Hg)		
	156 ± 24	–
Baseline		
	75 ± 19	–
Systolic		
Diastolic		
		–
Follow-up		
	134 ± 20	–
Systolic		
	70 ± 19	
Diastolic		
Hemoglobin (g/dL)		–
	10.6 ± 2.0	–
Baseline		
	11.2 ± 1.4	
Follow-up		
Heart Failure		–
	0/13	–
Baseline		
	1/13	
Follow-up		

* Data are expressed as mean ± standard deviation.

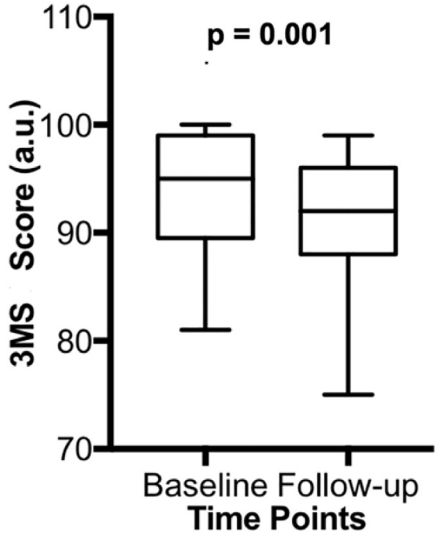

Fig. 1. Baseline and 6-month follow-up 3MS scores from hemodialysis patients.

4. Discussion

Brain perfusion is a critical physiological parameter associated with brain metabolism, reflecting brain tissue viability. An understanding of the characteristics of CBF, especially changes after hemodialysis initiation, may provide valuable insights into the origins of increased CI prevalence and stroke incidence in older hemodialysis patients. To our knowledge, this is the first prospective longitudinal ASL brain perfusion study to investigate CBF changes in older ESRD patients who transitioned to maintenance hemodialysis, and to perform rigorous CBF quantification using individually estimated T_{1B} values based on longitudinal measurements of hemoglobin levels to compensate for anemia effects on T_{1B}. Our longitudinal study results provide novel and direct evidence supporting the association between hemodialysis and progressive development of cerebrovascular dysfunction and associated cognitive decline in older hemodialysis patients. Further, our study adds evidence to a recent study that used transcranial Doppler and brain MRI in conjunction with longitudinal cognitive function to demonstrate longitudinal cerebrovascular changes after initiating hemodialysis and associated cognitive decline (Findlay et al., 2019).

4.1. CBF quantification for older hemodialysis patients and healthy control volunteers

Accurate CBF estimation relies on the accuracy of parameters used for the CBF quantification model. T_{1B} is a key parameter influencing CBF quantification, and can be significantly affected by hematocrit or hemoglobin levels. Hemoglobin level not only changes with age and sex, as indicated by this and other studies (Mahlknecht and Kaiser, 2010), but varies with degree of anemia, which is common in ESRD patients (Hsu et al., 2002; Astor et al., 2002; Fishbane and Spinowitz, 2018). To achieve rigorous CBF quantification, for hemodialysis patients we used estimated T_{1B} based on hemoglobin levels measured during baseline and follow-up visits to compensate for anemia effects; for controls, we employed estimated T_{1B} based on age- and sex-dependent hemoglobin levels reported in the literature (Mahlknecht and Kaiser, 2010).

4.2. Brain perfusion characteristics following hemodialysis initiation

Our study results confirm our hypothesis that CBF changes significantly approximately 6 months after hemodialysis initiation. Although only marginally significant CBF declines were observed globally in GM and WM (Fig. 2), significant CBF declines were found regionally in the hippocampus and orbitofrontal cortex (Fig. 3). These results are similar to findings from a previous cross-sectional ASL imaging study with populations of pre-hemodialysis and hemodialysis patients (Jiang et al., 2016). In addition, consistent with findings from our previous cross-sectional studies (Murray et al., 2006; Murray, 2008), significant longitudinal cognitive function decline was observed in this patient cohort (Fig. 1).

The observed declines in longitudinal CBF in hemodialysis patients are not likely because of hemoglobin and blood pressure changes across time. Our analyses indicated no significant difference between baseline and follow-up hemoglobin levels (Table 1), and no associations were found between changes in blood pressures and those in either global or regional CBF. During this pilot study, some patients changed the date for the initiation of their hemodialysis treatment, and others other could not perform the study at desired follow-up time point when patients were not feeling well, all of which made the time intervals between baseline and follow-up studies varied largely across patients. However, our statistical analyses suggest that such a variation of time intervals has no impact on our results, with no associations observed between the time intervals and the observed longitudinal perfusion changes. It is also unlikely that the observed CBF declines are due to normal aging. The magnitudes of the observed CBF decreases in our study were larger than age-related CBF changes reported in the literature. For example, the percentage change in mean global GM CBF in this study is about −4.8% per year, more than 10 times larger than reported age-related changes, which range from −0.38 to −0.45% per year (Biagi et al., 2007; Parkes et al., 2004; Wagner et al., 2012; Zhang et al., 2018).

The observed longitudinal CBF declines in hemodialysis patients may be due to reduced ability in compensatory cerebral vessel dilation. Similar to other studies (Zheng et al., 2016a, 2016b; Jiang et al., 2016; Kuwabara et al., 2002; Vorstrup et al., 1992; Hirakata et al., 1992;

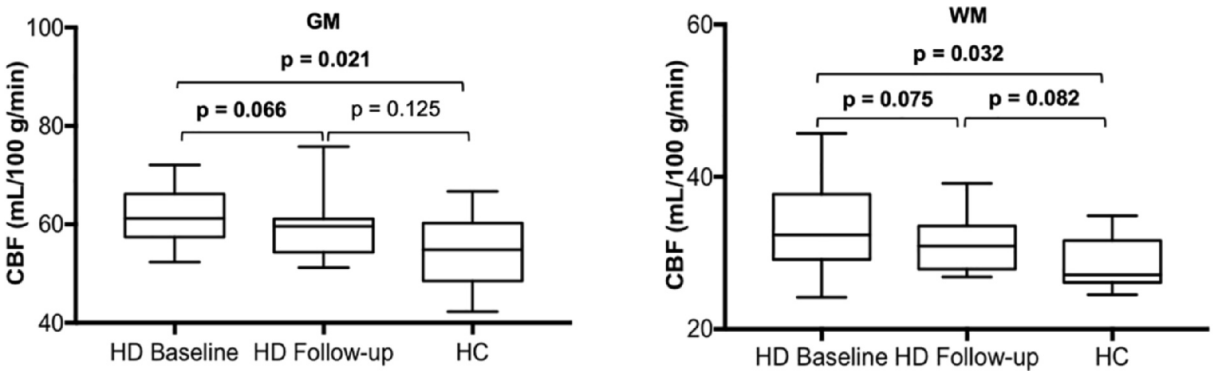

Fig. 2. Global cerebral blood flow (CBF) measurements in grey matter (GM) and white matter (WM) from hemodialysis (HD) patients and healthy control (HC) volunteers.

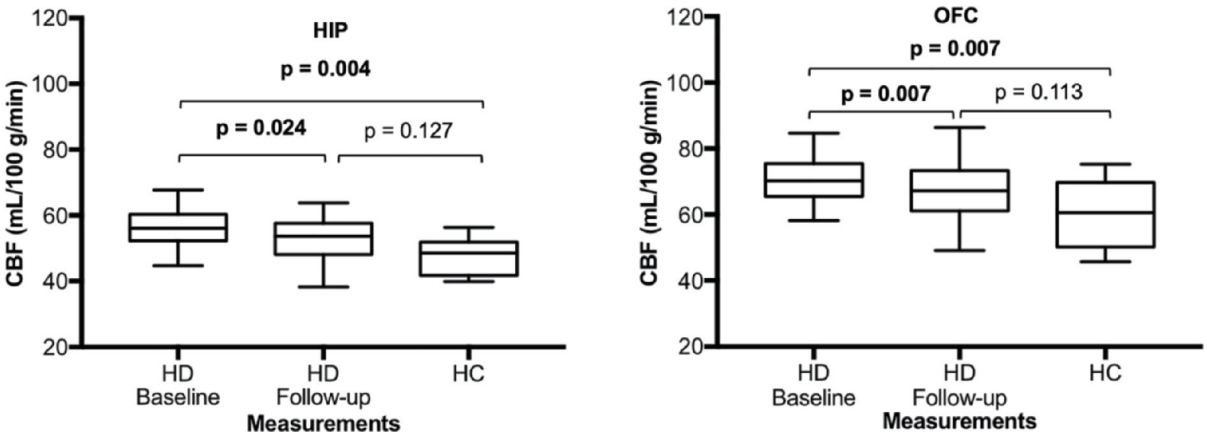

Fig. 3. Regional cerebral blood flow (CBF) measurements in the hippocampus (HIP) and orbitofrontal cortex (OFC) from hemodialysis (HD) patients and healthy control (HC) volunteers.

Mathew et al., 1985), our study showed that compared with age- and sex-matched healthy control volunteers, brain perfusion at baseline was significantly elevated for ESRD patients (Figs. 2 and 3). As this study also showed, ESRD patients have concomitant anemia, which can induce brain perfusion elevation via cerebral vessel dilation to compensate for anemia-associated reduced rate of oxygen delivery to brain tissue in order to maintain necessary brain metabolism and function. However, the circulatory stress of routine hemodialysis can also cause cerebral vasculature damage, or "brain stunning" especially in older ESRD patients (Findlay et al., 2019). The end results may be worsening endothelial dysfunction, negatively affecting cerebral vessel dilation as a compensation mechanism. A positron emission tomography (PET) study of CO_2 response with small cohorts of pre- hemodialysis and hemodialysis patients (Kuwabara et al., 2002) suggested reduced compensatory cerebral vessel dilation in hemodialysis patients. The reduced ability in compensatory cerebral vessel dilation can cause perfusion decline and inadequate oxygenation, and result in impaired CBF auto-regulation. This may explain the observed significant decline of cognitive function following hemodialysis initiation (Fig. 1).

Reduced brain metabolism may play a role in the observed longitudinal CBF declines in hemodialysis patients. One PET study with five normotensive hemodialysis patients and healthy control volunteers suggested that the metabolic rate of oxygen in hemodialysis patients was lower than in a control group (Hirakata et al., 1992). However, one recent MRI study found no significant differences between hemodialysis patients and healthy control volunteers regarding global oxygen metabolic rate (Zheng et al., 2016).

Although more studies are needed to investigate the underlying reasons for brain perfusion decline following hemodialysis initiation, the observed associations between longitudinal changes in 3MS score and regional CBF suggest that decreased brain perfusion may contribute to the observed cognitive decline.

5. Study limitations

Our study has several major limitations. First, the limited number of ESRD patients and healthy control volunteers in this pilot study reduced the power of our statistical analyses, and also made it challenging to perform voxel-based CBF analyses to detect subtle CBF differences or changes in specific brain regions containing small brain structures, such as the hippocampus that has varied shape and orientation across participants. Our findings, especially the observed associations between longitudinal changes in 3MS scores and regional CBF, need further verification with a larger number of patients and controls and utilizing voxel-based CBF analyses for more comprehensive results, as well as a follow-up study with healthy control volunteers to provide direct estimates of longitudinal CBF changes due to normal aging and hemoglobin levels. In addition, the 3MS test measures only global cognitive

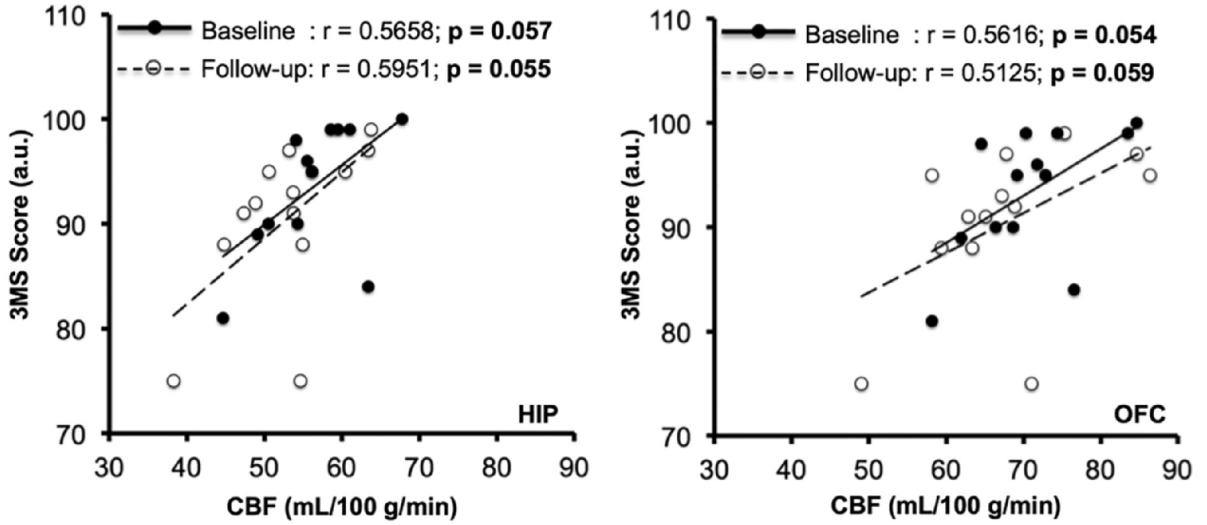

Fig. 4. Scatter plots of baseline and 6-month follow-up 3MS scores and CBF measurements in the hippocampus (HIP) and orbitofrontal cortex (OFC), and r represents Pearson correlation coefficient value.

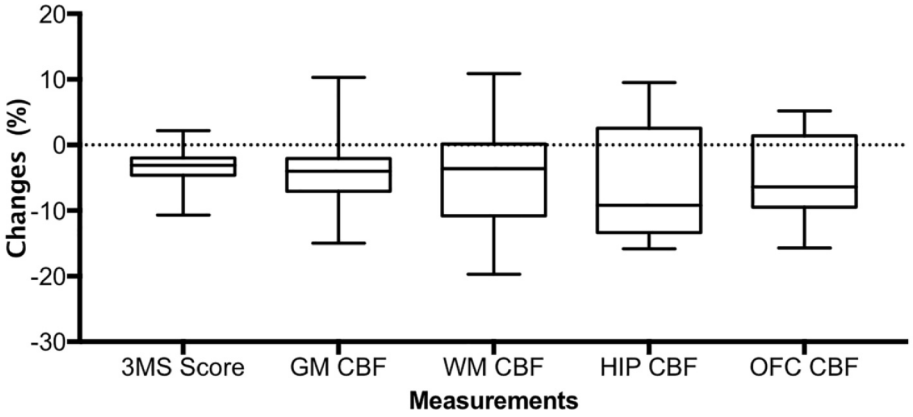

Fig. 5. Longitudinal percentage changes of 3MS scores and CBF measurements in GM, WM, the hippocampus (HIP), and orbitofrontal cortex (OFC), and r represents Pearson correlation coefficient value.

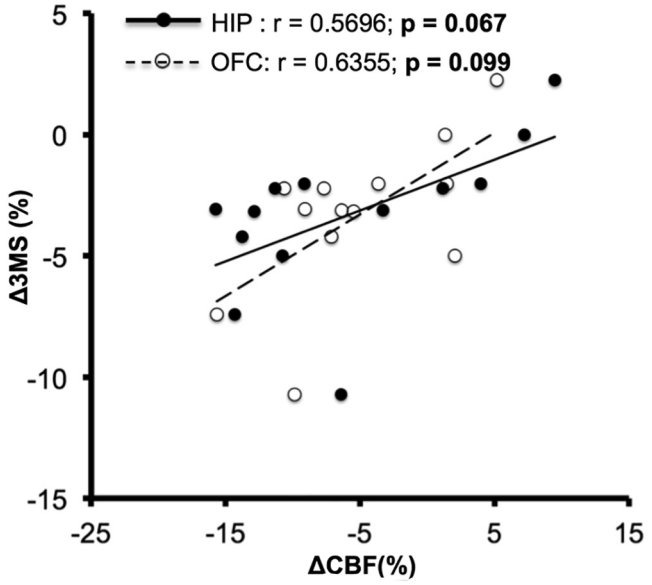

Fig. 6. Scatter plots of longitudinal percentage changes of 3MS scores and CBF measurements in the hippocampus (HIP) and orbitofrontal cortex (OFC), and r represents Pearson correlation coefficient value.

function. A full cognitive battery measuring domain-specific cognitive function would be more informative (e.g., decline in memory vs. executive function and associated region-specific changes in CBF) (Murray et al., 2016). We cannot exclude the possible effects of anemia medications such as ESAs or oral or IV iron on the ASL measures, which are not well defined in the literature. It is not possible to exclude dialysis patients on those medications, as they are standard of care. However, the hemoglobin levels, which are used to titrate these medications, did not vary significantly between visits, as noted in the results. Finally, there are limitations in our imaging methods. In this study, a relatively short post-bolus delay was applied, which may not be optimal for ASL imaging with old participants, and for more rigorous CBF quantification, multi-delay PCASL, in stead of single-delay pCASL, should have been applied to take care of the effects of arterial transit time differences between participants and across time. In addition, the use of low resolution for ASL imaging reduced the ability to obtain perfusion estimates in small brain structures, such as the hippocampus, which can be addressed in the future by using advanced image acquisition approaches designed for high-resolution ASL imaging (Li et al., 2015) at high magnetic field.

6. Conclusion

Following hemodialysis initiation, we found that CBF declined globally, although non-significantly, in GM and WM, and significantly regionally in the hippocampus and orbitofrontal cortex, paralleling the observed global cognitive decline. The associations between longitudinal changes in 3MS score and regional CBF suggest that decreased brain perfusion may contribute to the observed cognitive decline.

Declaration of Competing Interest

The authors declare that there is no conflict of interest associated with this manuscript.

CRediT authorship contribution statement

Xiufeng Li: Conceptualization, Methodology, Project administration, Investigation, Resources, Validation, Data curation, Formal analysis, Writing - original draft. **Yelena X. Slinin:** Methodology, Resources. **Lin Zhang:** Methodology, Formal analysis, Writing - review & editing. **Donald R. Dengel:** Methodology, Investigation. **David Tupper:** Methodology, Investigation. **Gregory J. Metzger:** Investigation, Resources, Writing - review & editing. **Anne M. Murray:** .

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