8-2022

The Relationship between Cerebrovascular Reactivity and Cerebral Oxygenation during Hemodialysis

W. T. Richerson
Marquette University

Brian D. Schmit
Marquette University, brian.schmit@marquette.edu

D. F. Wolfgram
Medical College of Wisconsin

Journal of the American Society of Nephrology (JASN), Vol. 33, No. 8 (2022): 1602-1612. DOI.

The Relationship between Cerebrovascular Reactivity and Cerebral Oxygenation during Hemodialysis

Wesley T. Richerson
Department of Biomedical Engineering, Marquette University and Medical College of Wisconsin, Milwaukee, Wisconsin
Brian D. Schmit
Department of Biomedical Engineering, Marquette University and Medical College of Wisconsin, Milwaukee, Wisconsin
Dawn F. Wolfgram
Department of Medicine, Medical College of Wisconsin and Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin

Abstract

Significance Statement

Patients with ESKD have a high burden of ischemic brain lesions related to decline in cerebral blood flow during hemodialysis. Preliminary studies in patients on hemodialysis noted impairment in cerebrovascular reactivity, a mechanism that regulates cerebral perfusion. We found that lower cerebrovascular reactivity was associated

with greater decrease in cerebral oxygen saturation during hemodialysis, particularly when accounting for changes in systemic BP. These results suggest that testing cerebrovascular reactivity could be relevant to characterizing risk of cerebral ischemia during hemodialysis and the potential sequelae of brain injury and cognitive impairment over time.

Background

Patients with kidney failure treated with hemodialysis (HD) may be at risk for cerebral hypoperfusion due to HD-induced BP decline in the setting of impaired cerebral autoregulation. Cerebrovascular reactivity (CVR), the cerebrovascular response to vasoactive stimuli, may be a useful indicator of cerebral autoregulation in the HD population and identify those at risk for cerebral hypoperfusion. We hypothesize that CVR combined with intradialytic BP changes will be associated with declines in cerebral oxygenation saturation (ScO_2) during HD.

Methods

Participants completed the MRI scans on a non-HD day and cerebral oximetry during HD. We measured CVR with resting-state fMRI (rs-fMRI) without a gas challenge and ScO_2 saturation with near-infrared spectroscopy. Regression analysis was used to examine the relationship between intradialytic cerebral oxygen desaturation, intradialytic BP, and CVR in different gray matter regions.

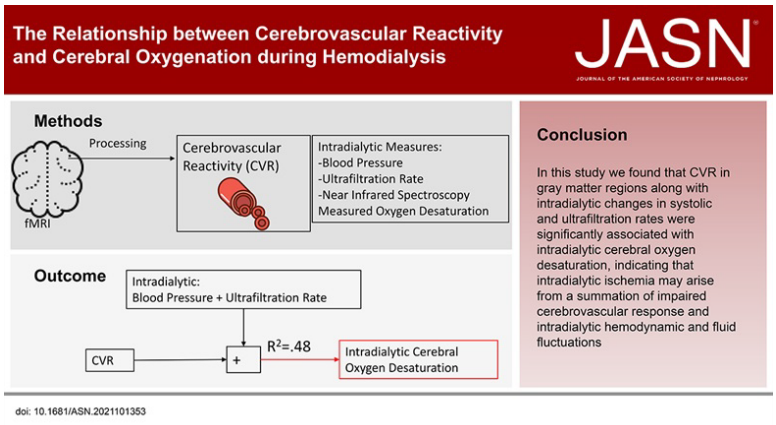
Results

Twenty-six patients on HD had complete data for analysis. Sixteen patients were men, 18 had diabetes, and 20 had hypertension. Mean±SD age was 65.3±7.2 years, and mean±SD duration on HD was 11.5±9.4 months. CVR in the anterior cingulate gyrus (ACG; P=0.03, r^2=0.19) and insular cortex (IC; P=0.03, r^2=0.19) regions negatively correlated with decline in intradialytic ScO_2. Model prediction of intradialytic ScO_2 improved when including intradialytic BP change and ultrafiltration rate to the ACG rsCVR (P<0.01, r^2=0.48) and IC rsCVR (P=0.02, r^2=0.35) models, respectively.

Conclusions

We found significant relationships between regional rsCVR measured in the brain and decline in intradialytic ScO_2. Our results warrant further exploration of using CVR in determining a patient's risk of cerebral ischemic injury during HD.

Visual Abstract



Introduction

Patients on hemodialysis (HD) have an increased burden of white matter disease and decreased gray matter volume when compared with controls; additionally patients on HD have worsening of white matter disease over

time relative to patients on HD who receive a transplant.[12–3] These white matter changes are often vascular in origin and are related to increased risk of cognitive impairment, stroke, dementia, and death.[4] It is hypothesized that structural changes in cerebral integrity are, in part, due to ischemic injury that occurs during HD due to impaired cerebrovascular response to systemic circulatory stress.[5] Intradialytic cerebral blood flow (CBF) and cerebral oxygen saturation (ScO_2) often decline in patients on HD, and may be affected by changes in BP.[2,67–8] Due to the rapid fluid removal and osmotic shifts that occur during HD, intradialytic drops in BP are common.[9] In a study measuring concurrent BP and ScO_2, BP changes were related to risk of cerebral ischemia, but there was no specific threshold of BP change, indicating the ScO_2 response to BP is varied and likely dependent on other patient characteristics.[8] Another study found no relationship between BP and CBF drops, as measured by positron emission tomography imaging, but this study was limited by a small cohort of 12 patients on HD.[6]

In normal physiology, the lack of change in cerebral perfusion during changes in systemic BP is attributed to cerebral autoregulation, a vasodilatory or constrictive response of the cerebral small vessels that aims to maintain constant cerebral perfusion.[10] However, patients on HD may have impaired cerebral autoregulation due to vascular disease that is inherent to renal disease and common comorbidities.[11] The cerebral autoregulatory response to hypotension induced during HD is reliant on vasodilatory capacity in the brain. Cerebral microvascular dilation can also be stimulated by increasing arterial Pco_2, by which cerebrovascular reactivity (CVR) occurs.[12] CVR is an indicator of the vasoregulatory capacity of the cerebral vasculature, which is a critical element of cerebral autoregulation. The codependence of cerebral autoregulation and CVR on the vasoregulatory capacity of the cerebral microvasculature is demonstrated when hypercapnia decreases the cerebral autoregulation response to hypotension, and *vice versa*.[10] Thus, CVR as a measure of vasoregulatory capacity may be an adequate surrogate marker for cerebral autoregulation function.

Recently CVR has been found to be impaired in patients on HD relative to controls and patients with CKD.[13] This impairment of CVR (acting as a marker for cerebral autoregulation function) may be an important factor in risk of decline in CBF during intradialytic hypotension.

In this study, we used an existing resting-state functional magnetic resonance imaging (rs-fMRI) dataset and a novel method to measure CVR on the basis of normal respiratory variation in carbon dioxide (CO_2) to calculate voxel-based resting state CVR (rsCVR) in patients on HD (full description in the *Methods* section).[14] Prior literature has noted that CVR measured using blood oxygen level dependent (BOLD) fMRI is predictive of white matter integrity deficits as measured by diffusion MRI, gray matter thickness, and white matter hyperintensity.[15,16] Thus, we investigated the relationship between rsCVR and the change in ScO_2 (ΔScO_2) during HD, and how the intradialytic hemodynamics may modify this relationship. We hypothesized that both cerebral microvascular responsiveness and change in BP during HD are likely important components in risk for cerebral ischemia. Our study may provide information on the pathophysiology of intradialytic cerebral hypoperfusion and cerebral ischemic injury in patients on HD.

Methods

Data for this cross-sectional study were obtained from an ongoing longitudinal study that included cerebral imaging and measurements of cognitive performance and patient-reported cognitive function data in a cohort of patients on HD at two time points, 1 year apart.[3] Cognitive measurements and fMRI data were used from one of the time points (depending on data availability) for this analysis, along with cerebral oximetry data obtained during an HD session. We attempted to obtain both the MRI and cognitive data within 2 weeks of the intradialytic cerebral oximetry data.

Participants

We recruited participants with ESKD treated with HD from four Milwaukee, Wisconsin area community dialysis units. Race and ethnicity were self-reported by each participant. Each participant with ESKD provided informed written consent to the protocol, which was approved by the Institutional Review Board at the Medical College of Wisconsin. Inclusion criteria were age ≥50 years and receiving thrice weekly conventional in-center HD. Participants also had to be on dialysis for >1 month but <2 years at enrollment. The 1-month cutoff was to avoid the complicating effects of untreated uremia, and the <2-years requirement was to capture the time at which cognitive changes may be more commonly occurring as part of a longitudinal study this cohort was completing. Exclusion criteria included a history of stroke, traumatic brain injury, brain tumor, or surgery within the past year; being non-English speaking; having hearing or vision impairment enough to preclude the ability to take the cognitive tests; and the presence of severe cognitive impairment that would prevent completing cognitive testing, or a diagnosis of dementia.

MRI

A GE Healthcare Discovery MR750 3T MRI with a 32-channel Nova Coil was used to collect images on the same day as the cognitive testing, immediately after the cognitive testing. No participant was given antianxiety or sedative medications for the scan. Every participant completed an MRI safety screen before the scan. T1-weighted anatomic images were acquired using an axial fast spoiled gradient recall 3D sequence (echo time=3.2 ms, repetition time=8.16 ms, flip angle=12°, prep time=450 ms, bandwidth=22.73 kHz, field of view=240 mm, 156 1-mm slices, matrix=256×240). The rs-fMRI sequence used echo planar imaging (echo time=25 ms, repetition time=2000 ms, flip angle=77°, field of view=224 mm, slice thickness=3.5 mm, matrix=64×64) to acquire 356 volumes in 11 minutes, 52 seconds.

Image Preprocessing

Anatomic T1 images were first bias corrected using the Advanced Normalization Tools (ANTs) N4 bias field correction function.[17] Bias-corrected anatomic images were then skull stripped using the robust brain extraction function.[18] Images were visually inspected to ensure full brain extraction, and then the FMRIB Software Library FAST algorithm was used to segment the T1 images into gray matter, white matter, and cerebral spinal fluid.[19] Finally, ANTs' SyN registration software was used to obtain a rigid, affine, and deformable transform between standard space and participant T1 anatomic space.[20]

rsCVR Processing

rs-fMRI images were processed using the same processing steps developed and validated in a study by Liu *et al.*,[14] which included healthy controls and a cohort with cerebrovascular disease (patients with Moyamoya disease). Liu *et al.*[14] were able to calculate CVR using no explicit gas challenge or breath holds from a typical rs-fMRI acquisition, but taking advantage of the effect that CO_2 fluctuations have on the global BOLD signal. They found good agreement with more traditional CVR methods using a CO_2 gas challenge (spatial correlation was 0.88 in controls and 0.71 in patients with Moyamoya disease). For this study, the first four volumes of the fMRI datasets were discarded to ensure signal stabilization. Then, the fMRI data were motion corrected using FMRIB Software Library's McFLIRT function and smoothed using an 8-mm full width at half maximum Gaussian kernel. The motion-corrected and smoothed data were then bandpass filtered at 0.02–0.04 Hz and detrended using the Analysis of Functional NeuroImages 3dBandpass function.[21,22] The ANTs SyN registration was used again to obtain the transform between resting-state space and T1 anatomic space.[20] The brain-extracted T1 image was then binarized and transformed into resting-state image space to mask the rs-fMRI data. The resulting rs-fMRI data were used to calculate a global BOLD signal consisting of an average of the 0.02–0.04 Hz signal across the brain volume. Note that the 0.02–0.04 Hz frequency band of the global BOLD signal is best correlated with end tidal CO_2.[14] The bandpass-filtered global BOLD signal was then used as a proxy for end tidal CO_2 in a general

linear model to predict the BOLD signal fluctuations in each voxel. The coefficient determining the relationship between the global BOLD signal and the voxel BOLD signal was defined as the rsCVR for each voxel. Gray matter and white matter masks in T1 image space were then transformed into resting-state image space to extract the mean rsCVR of these brain regions in each participant. rsCVR values were then normalized by the mean rsCVR by dividing each voxel rsCVR by the mean rsCVR across the brain in each participant. Finally, the Harvard-Oxford cortical atlas was transformed from standard Montreal NeuroIogical Institute space to resting-state image space using both the standard to anatomic transform and the anatomic to resting-state space transforms. rsCVR was averaged within each cortical region for statistical analysis.[23] rsCVR maps were then inspected to identify participants with lateralized deficits, which were removed as outliers for further analysis.

Cerebral Oximetry

Intradialytic ScO_2 was measured using near-infrared spectroscopy (NIRS) with the Nonin SenSmart X-100 Universal Oximetry System. NIRS is a valid method to detect change in CBF with significant correlation (r=0.56) between change in NIRS measurement and change in flow of middle cerebral artery, along with high specificity (100%) and sensitivity (88%).[24] Two regional oximetry probes were secured to the left and right sides of the participant's forehead during the HD session, and the probes recorded the blood oxygen saturation percentage every 4 seconds from the start to the end of HD treatment. The starting (baseline) ScO_2 was the average of the first 15 readings (1 minute) before the start of HD for both the right and left side. The ΔScO_2 during HD was calculated as the percentage difference in the area under the curve of the actual ScO_2 over the entire HD session (time) compared with the area under the curve for a theoretically stable ScO_2 over the same amount of time. This was done for both the right and left side. If the ScO_2 remained stable, increased, or decreased, this was defined as a zero, negative, or positive decline, respectively. We averaged the left and right ΔScO_2 from each HD session. To compare our ScO_2 changes to studies measuring changes in CBF, we also calculated the relative drop in ScO_2 using the baseline value minus the minimum value during the HD session, divided by the starting ScO_2 value. Due to technical issues with sensors not working or interference in the signal, some sessions had only one side of usable data; in these cases, we used the decline in that one side as the outcome variable.

Intradialytic Hemodynamic Variables

For the HD session in which we measured the ScO_2, we also collected the oscillometric systolic BPs (SBPs) and diastolic BPs (DBPs) that were taken at the start, every 30 minutes, and end of each session as standard of care. The change in BP during HD was measured as the post-HD starting BP minus the pre-HD BP. The ultrafiltration rate (UFR) for the HD session was the milliliter per kilogram per hour of fluid removed.

Cognitive Testing

Each participant completed the National Institutes of Health (NIH) Toolbox Cognition Battery, which includes seven assessments evaluating language, attention, processing speed, executive function, working memory, and episodic memory, along with three composite scores of fluid cognition (incorporating tests of executive function, memory, processing speed, and attention), crystallized cognition (incorporating language tests), and total cognition.[25] See Table 1 for a list of tests and corresponding cognitive domain. Testing was done the day after the participant's second dialysis session of the week. This was to avoid the immediate changes in cognition that can occur during and immediately after a dialysis session.[26] All testing was completed on an iPad while in a quiet room with a test administrator present.

Table 1. - Cognitive tests, corresponding cognitive domain, cohort scores, and P values for correlation with ΔScO_2

Cognitive Test	**Cognitive Domain Tested**	**Mean (SD)**	**Model *P* Value**
Picture Vocabulary Test	Language	104.3 (12.8)	0.05

Flanker Inhibitory Control and Attention Test	Attention and executive function	86.1 (10.0)	0.33
List Sorting Test	Working memory	92.8 (10.7)	0.89
Dimension Change Card Sort Test	Executive function	90.8 (13.8)	0.17
Pattern Comparison Processing Speed Test	Processing speed	79.0 (16.7)	0.11
Oral Reading Recognition	Language	104.3 (10.2)	0.22
Picture Sequence Memory Test	Episodic memory	91.5 (11.6)	0.65
Fluid Intelligence (combined)	N/A	82.8 (13.3)	0.04
Crystallized Intelligence (combined)	N/A	104.3 (11.7)	0.09
Total Intelligence (combined)	N/A	91.9 (13.8)	0.02

N/A, not applicable.

Statistical Analysis

The statistical analysis examined the relationship between rsCVR and ScO_2. We focused on the rsCVR values of Harvard-Oxford cortical atlas regions within and adjacent to the default mode network, a resting-state network in which reduced CVR was demonstrated in the underlying brain regions in patients with vascular risk factors (see Table 2 for regions tested).[23,27] Univariate linear regression models were run between the rsCVR of each Harvard-Oxford atlas region and the ScO_2 during HD. If the correlation was significant for a certain region, the region was also tested in a multiple linear regression model with both intradialytic DBP changes, intradialytic SBP changes, and UFR. Models were considered significant if $P<0.05$; these results are best used for hypothesis generating and thus we did not correct for multiple comparisons.

Table 2. - Harvard-Oxford cortical atlas regions tested that are within or adjacent to the DMN on the basis of the Yeo seven-network parcellation of the brain, with *P* values for correlation with ΔScO_2 during HD all significant relationships have a (+), denoting a positive correlation, or (−), denoting a negative correlation

Harvard-Oxford Cortical Region	**Model *P* Value**
Frontal pole	0.92
Paracingulate gyrus	0.16
Anterior cingulate gyrus (−)	0.03[a]
Posterior cingulate gyrus	0.57
Angular gyrus	0.29
Temporal pole	0.88
Inferior frontal gyrus	0.18
Frontal orbital cortex	0.99
Insular cortex (−)	0.03[a]
Parahippocampal anterior	0.88
Parahippocampal posterior (−)	0.02[a]
Precuneous cortex (+)	0.04[a]

Precuneous cortex was significant, but the coefficients sign was positive, opposite of what would be expected. All other significant relationships were negative, indicating that lower rsCVR was associated with higher decrease in ScO_2.

[a]Significant coefficient, $P<0.05$.

Results

Participants

Thirty-two patients on HD consented to participate. Subsequently, three participants withdrew because they could not arrange transportation to the off-site MRI, five were unable to get the MRI due to MRI screening failure or claustrophobia, one subject had an incomplete resting-state scan, one subject had lateralized deficits in the rsCVR map, one subject had excessive motion during the rs-fMRI, one subject was excluded due to an abscess that was surgically removed which left a visible surgical path on imaging, and one subject was excluded due to an incidental finding of multiple strokes that led to rsCVR values that were statistically noted as outliers. We included 26 participants on HD in the analysis. Demographics, including age, race, and sex, and medical comorbidities are noted in Table 3. On average, participants completed the MRI and cognitive testing within 15 days of the HD session when cerebral oximetry measure was completed.

Table 3. - Cohort demographics

Characteristics of Participants on HD (*n*=26)	**Value**
Age, mean (SD)	66.3 (7.2)
Male, *n* (%)	16 (61.5)
HD duration, mo, mean (SD)	11.5 (9.4)
SBP change, mm Hg, mean (SD)	−4.7 (16.9)
DBP change, mm Hg, mean (SD)	−1.8 (9.0)
UFR, ml/kg per hr, mean (SD)	9.8 (4.2)
ΔScO_2 during HD (% change in area under the curve), mean (SD)	−3.0 (3.3)
Relative drop in ScO_2 during HD (%), mean (SD)	10.1 (5.8)
Comorbidities, *n* (%)	
Hypertension	20 (76.9)
Diabetes	18 (69.2)
Coronary artery disease	9 (34.6)
Peripheral vascular disease	3 (11.5)
Congestive heart failure	8 (30.8)
Race, *n* (%)	
White	14 (53.9)
Black	9 (34.6)
Other	3 (11.5)
Cause of ESKD, *n* (%)	
Diabetes	14 (53.9)
Hypertension	5 (19.2)
Other	7 (26.9)
Educational level, *n* (%)	
High school or less	10 (38.5)
Some college/bachelor degree	11 (42.3)
Advanced degree	5 (19.2)

rsCVR and Relationship with ΔScO_2 during HD

Group-averaged rsCVR for our cohort can be seen in Figure 1, where the higher CVR in the gray matter and lower CVR in the white matter confirmed expected outcomes of the analysis and provided validation of the methodology. Of the regions tested, the anterior cingulate gyrus (P=0.03, r^2=0.19), insular cortex (P=0.03, r^2=0.19), and posterior parahippocampal gyrus (P=0.02, r^2=0.20) regions were significantly correlated with a decline in ScO_2 during HD. The relationships between rsCVR of the anterior cingulate gyrus and insular

cortex with ΔScO_2 during HD are shown in Figures 2 and 3, respectively. In all three regions (anterior cingulate gyrus, insular cortex, and posterior parahippocampal gyrus), a negative slope was observed in which participants with greater intradialytic oxygen desaturation exhibited lower rsCVR. The insets in Figures 2 and 3 display images of the anatomic regions, with darker colors indicating lower rsCVR.

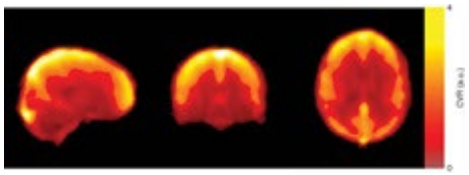


Figure 1.: Images of the brain demonstrating differences in group-averaged rsCVR using a heat map. Yellow/white indicates a high rsCVR, and dark red is a low or negligible rsCVR. The higher CVR in gray matter and lower CVR in white matter is expected and provides validation of the rsCVR methodology.

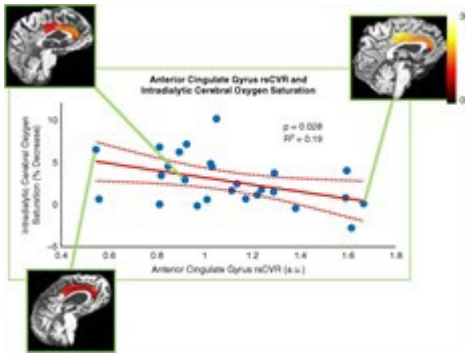


Figure 2.: Lower anterior cingulate gyrus rsCVR is associated with greater decrease in intradialytic ScO 2 . Individual subject brains with anterior cingulate gyrus rsCVR overlaid on T1-weighted anatomic scans. Scales for all rsCVR overlays were from zero to three.

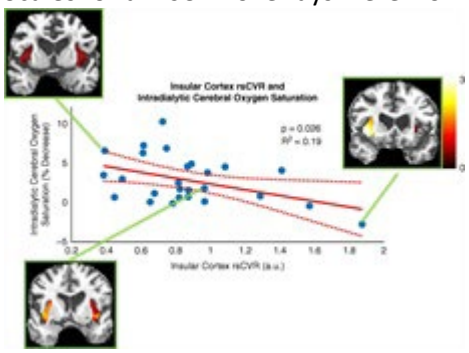


Figure 3.: Lower insular cortex rsCVR is associated with greater decrease in intradialytic ScO 2 . Individual subject brains with insular cortex rsCVR overlaid on T1-weighted anatomic scans. Scales for all rsCVR overlays were from zero to three.

rsCVR and Relationship with ΔScO_2 during HD Including Hemodynamic Variables

Adding the change in SBP slightly improved the models for the anterior cingulate gyrus (P=0.008, r^2=0.35) and insular cortex (P=0.03, r^2=0.26). The coefficient for the change in SBP variable was negative, indicating a greater decrease in SBP was associated with greater decline in ScO_2. The change in DBP did not improve the relationship between rsCVR and change in ScO_2. To further test intradialytic hemodynamic effects on ScO_2, UFR was added to each significant model. With the UFR added, the anterior cingulate gyrus (P=0.01, r^2=0.32) and insular cortex (P=0.02, r^2=0.29) rsCVR models improved. The posterior parahippocampal gyrus rsCVR and UFR model remained borderline significant (P=0.05, r^2=0.24). Including both UFR and SBP changes in the anterior cingulate gyrus model significantly improved the model (P=0.002, $r2$=0.48), whereas adding UFR and SBP changes to the insular cortex model had a slight improvement compared with including change in SBP alone (P=0.02, $r2$=0.35), see Table 4.

Table 4. - Regression models tested on the basis of the three regions' rsCVRs that were significantly related to cerebral oxygen desaturation during dialysis. Numbers in the parentheses are the 95% confidence intervals of the linear regression coefficient

rsCVR Predictor	Predictor 2	Predictor 3	Model *P* Value	R^2
Anterior cingulate gyrus (−7.8, −0.5)[a]	—	—	0.03	0.19
Anterior cingulate gyrus (−8.8, −1.8)[a]	SBP change (−0.14, −0.01)[a]	—	0.008	0.35
Anterior cingulate gyrus (−8.1, −1.2)[a]	UFR (−0.51, −0.01)[a]	—	0.01	0.32
Anterior cingulate gyrus (−9.0, −2.5)[a]	SBP change (−0.48, −0.03)[a]	UFR (−0.48, −0.03)[a]	0.002	0.48
Insular cortex (−6.8, −0.5)[a]	—	—	0.03	0.19
Insular cortex (−6.7, −0.5)[a]	SBP change (−0.11, 0.01)	—	0.03	0.26
Insular cortex (−6.7, −0.7)[a]	UFR (−0.47, 0.03)	—	0.02	0.29
Insular cortex (−6.7, −0.7)[a]	SBP change (−0.10, 0.02)	UFR (−0.46, 0.04)	0.02	0.35
Parahippocampal posterior (−10.7, −0.9)[a]	—	—	0.02	0.20
Parahippocampal posterior (−10.3, −0.2)[a]	SBP change (−0.10, 0.04)	—	0.05	0.23
Parahippocampal posterior (−10.16, 0.02)	UFR (−0.41, 0.14)	—	0.05	0.24
Parahippocampal posterior (−9.8, 0.8)	SBP change (−0.10, 0.04)	UFR (−0.42, 0.14)	0.08	0.26
Precuneous (0.08, 5.0)[a]	—	—	0.04	0.16
Precuneous (−0.22, 4.0)	SBP change (−0.10, 0.03)	—	0.08	0.20
Precuneous (−0.05, 4.83)	UFR (−0.46, 0.07)	—	0.05	0.23
Precuneous (−0.33, 4.6)	SBP change (−0.10, 0.03)	UFR (−0.45, 0.08)	0.07	0.27

Numbers in the parentheses are the 95% confidence intervals of the linear regression coefficient.
[a]Significant coefficient, $P<0.05$.

NIH Cognition Battery Outcomes

In general, scores of the Flanker Inhibitory Control and Attention Test and Pattern Comparison Processing Speed Test were lower compared with the normal population mean±SD of 100±15, see Table 1. These tests assess the cognitive domains of executive function, attention, and processing speed. Lower total and fluid intelligence scores were significantly associated with greater decline in ScO_2 during HD (P=0.02, r^2=0.21 and P=0.04, r^2=0.17, respectively). No other cognitive tests in the NIH Toolbox were correlated with ΔScO_2. No relationship was found between any cognitive test scores and rsCVR, BP change, or UFR.

Discussion

Our study investigated risk factors for cerebral ischemic injury during HD, focusing on the role of CVR and hemodynamic changes that occur during HD. In this study, we used rsCVR as a measure of vasoregulatory capacity, an important element of cerebral autoregulation, which is the mechanism that maintains CBF during systemic BP changes. We found that rsCVR in the anterior cingulate gyrus, insular cortex, and posterior parahippocampal gyrus were negatively related to ΔScO_2 during HD. The rsCVRs in those regions accounted for

approximately 18%–20% of the variance in intradialytic ScO_2. When change in SBP was added to the model, the anterior cingulate gyrus model predicted 35% of ΔScO_2 during HD, and further addition of UFR improved the model to explain about 48% of the variance. Our results indicate that ΔScO_2 may be affected by a combination of impaired vasoregulatory capacity, fluid fluctuations, and changes in BP. In addition, we found that greater decline in ScO_2 was associated with lower fluid intelligence and total intelligence, as measured by the NIH Toolbox Cognition Battery. A theoretic framework depicting the role of intradialytic drop in BP in the setting of impaired CBF control, leading to cerebral hypoperfusion and ischemic injury, is shown in Figure 4.

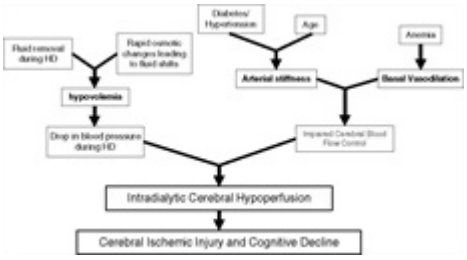


Figure 4.: Conceptual framework of HD-related cerebral ischemic injury and cognitive decline. Impaired CBF control is affected by increased arterial stiffness in the HD patient population, which is caused by increased rates of hypertension and type 2 diabetes along with older age. In addition to traditional risk factors for impaired blood flow control, patients on HD are more likely to be anemic, which causes baseline vasodilation to compensate for the decreased oxygen delivery. In this framework, it is proposed that a patient on HD may not be able to vasodilate their cerebral vasculature to compensate for the drops in BP arising from hypovolemia inherent to the HD therapy. Their risk for intradialytic hypoperfusion and subsequent cerebral ischemic injury increases and, in turn, may cause cognitive decline over time.

CVR as a Factor in Intradialytic CBF

The significant correlation between rsCVR and ΔScO_2 during HD is consistent with other reports of altered vasoregulatory capacity in patients on HD. Anemia secondary to renal failure can cause a baseline vasodilation in patients on HD relative to healthy controls, thereby exhausting vasodilatory capacity.[28,29,30–31] Further, the combination of conditions, such as diabetes, hypertension, older age, arteriosclerosis, vascular calcification, and high inflammatory state, that are common in patients with ESKD may lead to cerebrovascular stiffness, restricting the ability to vasodilate. Together, these factors impair the cerebral vasoregulatory response that is needed in both CVR and cerebral autoregulation, leading to decreases in CBF and associated hypoperfusion. Preliminary studies show that both CVR and cerebral autoregulation may be impaired in patients on HD.[11,13] Our model relating lower CVR with greater decline in ScO_2 during HD improved when accounting for the change in systemic BP during HD, suggesting it is the vasoregulatory response that is common to both CVR and cerebral autoregulation that is impaired. As an aside, we found that rsCVR in the precuneus cortex was positively associated with ΔScO_2 during HD, contrary to the observations in the other brain regions; however, that relationship was no longer significant when adding change in SBP or UFR to the model, indicating some other confounding effect. It should be noted that CVR may be different during HD due to the changes in pH that occur during HD and the effect of bicarbonate on vasodilation. However, cerebral CVR measures made outside of the HD session still provide estimates of baseline vasoregulatory function, accounting for underlying vascular disease and anemia effects on cerebral vasodilation. In the HD population with significant vascular disease, CVR measures are likely an adequate surrogate for gauging the cerebral autoregulatory response.

Similar to CVR, cerebral autoregulation may also fluctuate during HD due to cerebral fluid and osmotic shifts that can affect intracranial pressure and subsequently affect cerebral prefusion pressure.[32] Cerebral autoregulation response can vary in patients with traumatic brain injury and critical illness, and, in some circumstances, intact cerebral autoregulation may not reduce risk of change in CBF.[33,34–35] The cerebral vascular response is complex and, in our study, including BP and fluid removal explain only a portion of the ΔScO_2 during

HD. Additional explanatory factors that could affect ΔScO_2 during HD include factors that affect vasodilation, such as change in serum bicarbonate levels and hematocrit that can occur during HD; factors that may affect intracranial pressure, including fluid, electrolyte, and osmotic shifts during HD; markers of cerebral metabolism; and the severity of vascular disease risk factors, such as degree of BP, glycemic, and serum phosphate level control, that may affect vascular stiffness.

CVR in Patients on HD

CVR has been studied in a small cohort of patients on HD with some variability in results.[13,28,3637–38] The differences between studies may be due to the different modalities of measuring CBF, the type of CO_2 stimulus, and the age of the patient group. Using positron emission tomography, Kuwabara *et al.*[38] found a decreased CVR in response to 5% CO_2 inspiration in patients on HD and that the CVR was related to baseline CBF and hematocrit levels. However, the study only included five patients on HD and five patients with pre-HD ESKD.[38] In contrast, using transcranial Doppler and a rebreathing CO_2 stimulus, Skinner *et al.*[37] found that CVR was within a normal range and did not change from pre- to post-HD session. However, the study did not include a control group, the mean age of the study group was 44 years with no participants >60 years, anemia was mild if present, and patients with diabetes (a vascular disease risk factor) were excluded.[37] These characteristics are different from the general characteristics of the HD population in the United States. In a small but more age-relevant cohort, Slessarev *et al.*[13] found that patients on HD have an impaired CVR when compared with both healthy controls and patients with predialysis CKD. Thus, in patients on HD more similar in age and comorbidity to our study participants, impaired CVR is more common and is likely a relevant risk factor for cerebral hypoperfusion.

Cognitive Outcomes

Although we noted a relationship between CVR and ΔScO_2 during HD, we did not find a relationship between CVR and our measures of cognitive function using the NIH Toolbox Cognition Battery. A large study in patients without renal failure showed that whole-brain CVR was associated with performance on global cognition tests and that approximately 13% lower CVR was noted in those with impaired cognition versus those with normal cognition, demonstrating that small changes in CVR may affect cognition.[39] The lack of a significant relationship in our cohort may be a limitation of sample size or may indicate that other factors, alone or in combination with CVR, likely underlie cognitive losses in patients on HD. Interestingly, we found that greater decreases in ScO_2 during HD were associated with worse cognitive tests scores of fluid intelligence and global cognition. This supports the contribution of cerebral hypoperfusion during HD to cerebral injury and cognitive dysfunction. The relationship between markers of CBF and cognitive function was also noted by others, suggesting that intradialytic ischemia produces brain injury, which can lead to cognitive impairment.[2,8] In the study by Findlay *et al.*,[2] the decline in CBF during HD, as measured by transcranial Doppler, was 10%, which is similar to our relative decrease of 10% in ScO_2 during HD, reinforcing the concept that changes of this magnitude in markers of cerebral perfusion may affect cognitive outcomes. We did not measure the oximetry and cognitive measurements concurrently and note that both measures can vary; in particular, cognitive scores are noted to vary from pre- to intra- to post-HD.[26] However, all cognitive measures were performed the day after the midweek HD session to avoid variation from the timing in relation to the HD session, and should better reflect baseline cognitive function. Thus, we interpret our results as demonstrating a relationship between participants who are likely to have cerebral hypoperfusion during HD and their baseline cognitive status, but acknowledge the complex nature of this relationship that may vary on the basis of timing of measurements.

In evaluating the regions where rsCVR was associated with ΔScO_2 during HD, we note that the insular cortex and anterior cingulate gyrus are part of the cingulo-opercular resting-state network, a network in which lower connectivity is associated with lower NIH Toolbox fluid cognition scores.[40] The cingulo-opercular network is a major cognitive control network and is thought to be involved in processes that include attending to stimuli, formulating a response, and adapting to feedback. This information could tie together our results of the

significant relationship between the fluid and total NIH Toolbox cognition scores with ΔScO_2 during HD and the significant relationship between ΔScO_2 during HD and rsCVR in anterior cingulate gyrus and insular cortex.

Limitations

Although our cohort was larger than most studies evaluating CVR in patients on HD, our analysis is still limited by the small sample and our results should be viewed as hypothesis generating rather than confirmatory. We hope our methodology and investigation can help further research in this area. Second, we did not have a direct measure of cerebral autoregulation, which would be a more relevant predictor of ΔScO_2 during HD due to the role of systemic BP; however, we do provide the premise for using CVR as a marker of vasoregulatory capacity, which is an important component of cerebral autoregulation. Whereas our measure of rsCVR has been shown to be reliable and replicable in healthy controls and patients with Moyamoya disease,[14] a stimulated change in CVR would likely have provided a more accurate CVR measurement. Third, using standard-of-care intervals for measuring BP limits time resolution and may miss BP changes that occur between the 30-minute intervals. Our finding of a relationship with this less-sensitive BP measure demonstrates that the relationship between systemic hemodynamics and cerebral perfusion warrants further study. Using continuous beat-to-beat BP monitoring would likely increase sensitivity in measuring a relationship between systemic BP and cerebral distress and should be considered in future studies. Fourth, with only one cognitive assessment in our cohort, cognitive scores are subject to subjective factors, such as how the participant was feeling that day, and may not be a reliable indicator of their usual cognitive function. Finally, our indicator of cerebral perfusion was ScO_2. Although this has the advantage of continuous monitoring during the entire HD session, it is an indirect and less sensitive marker of cerebral perfusion and has spatial limitations associated with the two forehead sensors. This more superficial monitoring of ScO_2 limits our ability to detect ischemia where white matter hyperintensities develop, in the deep and periventricular white matter. However, it is not unreasonable to think that ischemia detected at the cortex could indicate similar or worse ischemia in the deep white matter, because deep white matter is more susceptible to chronic hypoperfusion due to its position at the border between the vascular territories of the anterior and middle cerebral arteries.[41]

In this study, we found that rsCVR in gray matter regions of the anterior cingulate gyrus and insular cortex and intradialytic changes in SBP and UFR were significantly associated with ΔScO_2 during HD. This indicates that impaired CVR in patients on HD paired with intradialytic SBP changes may be key factors in the intradialytic declines in CBF that are known to occur in some patients during HD. Our preliminary results should be used to guide a larger study that can confirm these results; use more explicit stimuli to measure CVR in patients on HD; clarify the roles of basal vasodilation, anemia, and bicarbonate in impairing or enhancing CVR in patients on HD; and continue investigation of the effect of CVR on both the change in brain structure and measures of cognition. Future work may lead to a more clinically applicable method to measure CVR, with the aim to use it as part of clinical care to help identify patients at higher risk of cerebral ischemic injury during HD, provide better prognostic information for patients, and allow for better recommendations for dialysis modalities that mitigate risk of cerebral injury.

Disclosures

B.D. Schmit reports having patents or royalties with Case Western Reserve University. All remaining authors have nothing to disclose.

Funding

This work was supported by National Center for Advancing Translational Sciences grant TL1TR001437 and NIH National Institute of Diabetes and Digestive and Kidney Diseases grant 5K23DK113119.

Published online ahead of print. Publication date available at www.jasn.org.

Author Contributions

W.T. Richerson wrote the original draft and was responsible for formal analysis; W.T. Richerson and D.F. Wolfgram conceptualized the study; B.D. Schmit was responsible for resources; B.D. Schmit and D.F. Wolfgram reviewed and edited the manuscript and provided supervision; and D.F. Wolfgram was responsible for data curation, funding acquisition, and investigation.

Data Sharing Statement

All data are included in the manuscript and/or supporting materials.

References

1. Fazekas G, Fazekas F, Schmidt R, Kapeller P, Offenbacher H, Krejs GJ: Brain MRI findings and cognitive impairment in patients undergoing chronic hemodialysis treatment. J Neurol Sci 134: 83–88, 1995
2. Findlay MD, Dawson J, Dickie DA, Forbes KP, McGlynn D, Quinn T, et al.: Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients. J Am Soc Nephrol 30: 147–158, 2019
3. Richerson WT, Umfleet LG, Schmit BD, Wolfgram DF: Changes in cerebral volume and white matter integrity in adults on hemodialysis and relationship to cognitive function. Nephron 145: 35–43, 2021
4. Debette S, Schilling S, Duperron MG, Larsson SC, Markus HS: Clinical significance of magnetic resonance imaging markers of vascular brain injury: A systematic review and meta-analysis. JAMA Neurol 76: 81–94, 2019
5. McIntyre CW: Recurrent circulatory stress: The dark side of dialysis. Semin Dial 23: 449–451, 2010
6. Polinder-Bos HA, García DV, Kuipers J, Elting JWJ, Aries MJH, Krijnen WP, et al.: Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. J Am Soc Nephrol 29: 1317–1325, 2018
7. Polinder-Bos HA, Elting JWJ, Aries MJ, García DV, Willemsen AT, van Laar PJ, et al.: Changes in cerebral oxygenation and cerebral blood flow during hemodialysis - A simultaneous near-infrared spectroscopy and positron emission tomography study. J Cereb Blood Flow Metab 40: 328–340, 2020
8. MacEwen C, Sutherland S, Daly J, Pugh C, Tarassenko L: Relationship between hypotension and cerebral ischemia during hemodialysis. J Am Soc Nephrol 28: 2511–2520, 2017
9. McIntyre CW, Goldsmith DJ: Ischemic brain injury in hemodialysis patients: Which is more dangerous, hypertension or intradialytic hypotension? Kidney Int 87: 1109–1115, 2015
10. Willie CK, Tzeng YC, Fisher JA, Ainslie PN: Integrative regulation of human brain blood flow. J Physiol 592: 841–859, 2014
11. Wolfgram DF, Novotny J, Goodman MJ, Visotcky A, Laud P, Barnes JN: Risk factors for intradialytic decline in cerebral perfusion and impaired cerebral autoregulation in adults on hemodialysis. Hemodial Int 26: 48–56, 2022
12. Sleight E, Stringer MS, Marshall I, Wardlaw JM, Thrippleton MJ: Cerebrovascular reactivity measurement using magnetic resonance imaging: A systematic review. Front Physiol 12: 643468, 2021
13. Slessarev M, Mahmoud O, Albakr R, Dorie J, Tamasi T, McIntyre CW: Hemodialysis patients have impaired cerebrovascular reactivity to CO_2 compared to chronic kidney disease patients and healthy controls: A pilot study. Kidney Int Rep 6: 1868–1877, 2021
14. Liu P, Li Y, Pinho M, Park DC, Welch BG, Lu H: Cerebrovascular reactivity mapping without gas challenges. Neuroimage 146: 320–326, 2017
15. Sam K, Crawley AP, Poublanc J, Conklin J, Sobczyk O, Mandell DM, et al.: Vascular dysfunction in leukoaraiosis. AJNR Am J Neuroradiol 37: 2258–2264, 2016

16. Fierstra J, Poublanc J, Han JS, Silver F, Tymianski M, Crawley AP, et al.: Steal physiology is spatially associated with cortical thinning. J Neurol Neurosurg Psychiatry 81: 290–293, 2010
17. Tustison NJ, Avants BB, Cook PA, Zheng Y, Egan A, Yushkevich PA, et al.: N4ITK: Improved N3 bias correction. IEEE Trans Med Imaging 29: 1310–1320, 2010
18. Iglesias JE, Liu CY, Thompson PM, Tu Z: Robust brain extraction across datasets and comparison with publicly available methods. IEEE Trans Med Imaging 30: 1617–1634, 2011
19. Zhang Y, Brady M, Smith S: Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imaging 20: 45–57, 2001
20. Avants BB, Epstein CL, Grossman M, Gee JC: Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. Med Image Anal 12: 26–41, 2008
21. Cox RW, Hyde JS: Software tools for analysis and visualization of fMRI data. NMR Biomed 10: 171–178, 1997
22. Cox RW: AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29: 162–173, 1996
23. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al.: An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31: 968–980, 2006
24. Al-Rawi PG, Smielewski P, Kirkpatrick PJ: Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. Stroke 32: 2492–2500, 2001
25. Heaton RK, Akshoomoff N, Tulsky D, Mungas D, Weintraub S, Dikmen S, et al.: Reliability and validity of composite scores from the NIH Toolbox Cognition Battery in adults. J Int Neuropsychol Soc 20: 588–598, 2014
26. Murray AM, Pederson SL, Tupper DE, Hochhalter AK, Miller WA, Li Q, et al.: Acute variation in cognitive function in hemodialysis patients: A cohort study with repeated measures. Am J Kidney Dis 50: 270–278, 2007
27. Haight TJ, Bryan RN, Erus G, Davatzikos C, Jacobs DR, D'Esposito M, et al.: Vascular risk factors, cerebrovascular reactivity, and the default-mode brain network. Neuroimage 115: 7–16, 2015
28. Zheng G, Wen J, Yu W, Li X, Zhang Z, Chen H, et al.: Anemia rather than hypertension contributes to cerebral hyperperfusion in young adults undergoing hemodialysis: A phase contrast MRI study. Sci Rep 6: 22346, 2016
29. Jiang XL, Wen JQ, Zhang LJ, Zheng G, Li X, Zhang Z, et al.: Cerebral blood flow changes in hemodialysis and peritoneal dialysis patients: An arterial-spin labeling MR imaging. Metab Brain Dis 31: 929–936, 2016
30. Vorstrup S, Lass P, Waldemar G, Brandi L, Schmidt JF, Johnsen A, et al.: Increased cerebral blood flow in anemic patients on long-term hemodialytic treatment. J Cereb Blood Flow Metab 12: 745–749, 1992
31. Sprick JD, Nocera JR, Hajjar I, O'Neill WC, Bailey J, Park J: Cerebral blood flow regulation in end-stage kidney disease. Am J Physiol Renal Physiol 319: F782–F791, 2020
32. Lund A, Damholt MB, Wiis J, Kelsen J, Strange DG, Møller K: Intracranial pressure during hemodialysis in patients with acute brain injury. Acta Anaesthesiol Scand 63: 493–499, 2019
33. Toth P, Szarka N, Farkas E, Ezer E, Czeiter E, Amrein K, et al.: Traumatic brain injury-induced autoregulatory dysfunction and spreading depression-related neurovascular uncoupling: Pathomechanisms, perspectives, and therapeutic implications. Am J Physiol Heart Circ Physiol 311: H1118–H1131, 2016
34. Slessarev M, Mahmoud O, McIntyre CW, Ellis CG: Cerebral blood flow deviations in critically ill patients: Potential insult contributing to ischemic and hyperemic injury. Front Med (Lausanne) 7: 615318, 2021

35. Rangel-Castilla L, Gasco J, Nauta HJ, Okonkwo DO, Robertson CS: Cerebral pressure autoregulation in traumatic brain injury. Neurosurg Focus 25: E7, 2008
36. Ishida K, Uchida M, Utada K, Yamashita A, Yamashita S, Fukuda S, et al.: Cerebrovascular CO_2 reactivity during isoflurane-nitrous oxide anesthesia in patients with chronic renal failure. J Anesth 32: 15–22, 2018
37. Skinner H, Mackaness C, Bedforth N, Mahajan R: Cerebral haemodynamics in patients with chronic renal failure: Effects of haemodialysis. Br J Anaesth 94: 203–205, 2005
38. Kuwabara Y, Sasaki M, Hirakata H, Koga H, Nakagawa M, Chen T, et al.: Cerebral blood flow and vasodilatory capacity in anemia secondary to chronic renal failure. Kidney Int 61: 564–569, 2002
39. Kim D, Hughes TM, Lipford ME, Craft S, Baker LD, Lockhart SN, et al.: Relationship between cerebrovascular reactivity and cognition among people with risk of cognitive decline. Front Physiol 12: 645342, 2021
40. Hausman HK, O'Shea A, Kraft JN, Boutzoukas EM, Evangelista ND, Van Etten EJ, et al.: The role of resting-state network functional connectivity in cognitive aging. Front Aging Neurosci 12: 177, 2020
41. Brown WR, Thore CR: Review: Cerebral microvascular pathology in ageing and neurodegeneration. Neuropathol Appl Neurobiol 37: 56–74, 2011