Hemodynamics During Dialysis and Changes in Cognitive Performance

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ABSTRACT

Introduction: Hemodialysis (HD) patients are at increased risk for cognitive impairment. Blood pressure (BP) fluctuations during HD may affect cerebral perfusion and subsequently cognitive function.

Objective: Examine and provide information on the relationship between intradialytic hemodynamics and cognitive outcomes over a 1-year period.

Methods: HD patients without diagnosed dementia who were 50 years old or older were given a neurocognitive battery at baseline and at 1-year follow-up. Over the 1-year period, we collected demographic and laboratory data, as well as dialytic BP and ultrafiltration rate (UFR) measurements and tested the association between changes in cognitive test scores and intradialytic hemodynamics, adjusting for demographic and clinical variables.

Results: Thirty-nine participants enrolled in the study and 32 remained at 1-year follow-up. The mean (SD) age was 66.8 (10.0) years. Hypertension was present in 100% and diabetes mellitus in 47% of the cohort. The average change in systolic BP from predialysis to postdialysis was -9.9 (16.3) mmHg, and average maximum drop in systolic BP during dialysis was 27.9 (10.2) mmHg. Overall, the cognitive test scores did not have significant changes from baseline to 1 year. In our linear regression analysis there was no association between the BP measures and cognitive changes, although UFR was associated with change in performance on a test of executive functioning.

Conclusions: In prevalent HD patients, cognitive function was generally stable over a 1-year period, and there was no association with intradialytic hemodynamic variables.

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INTRODUCTION

Cognitive impairment is common in patients receiving hemodialysis (HD) for end-stage renal disease (ESRD).[1] Among individuals with ESRD, cognitive impairment is associated with increased mortality and health care costs, and decreased quality of life.[2-4] Unfortunately, cognitive impairment appears to worsen in patients receiving HD. Furthermore, with our aging dialysis population, cognitive impairment may become more prevalent as age is a risk factor for cognitive decline. An analysis of United States Renal Data System data reveals a significant increase in incident dementia following initiation of HD, specifically when compared to patients with ESRD on peritoneal dialysis.[5] A small longitudinal study demonstrated that HD patients had greater decline in Mini-Mental Status Exam than age-matched controls.[6]

Beyond traditional risk factors, it is not clear why the HD population disproportionately experiences cognitive impairment. Although chronic kidney disease is associated with cognitive impairment,[7] aspects of the HD process may additionally contribute directly to cognitive decline.[1,8] Since HD is often characterized by large swings in blood pressure (BP),[9] it has been hypothesized that drops in BP may lead to periods of decreased cerebral perfusion, which cumulatively lead to ischemic injury, atrophy, and subsequent cognitive decline.[8,10] Previous studies using transcranial doppler monitoring have shown that cerebral blood flow decreases during HD.[11] Moreover, brain imaging of persons on HD reveals more atrophy, silent infarcts, and white matter disease than that of age-matched control subjects not on dialysis.[12,13]

We previously reported that there was no association between cognitive performance and intradialytic BP variability in a cross-sectional study.[14] However, given limitations of cross-sectional data, we conducted a 1-year prospective study to better character-

Table 1. Baseline Demographics and Characteristics of the Cohort

Variable	Mean (SD) or N (%)
Age (years)	66.8 (10.0)
Race	
White	8 (25.0)
African American	21(65.6)
Native American	2 (6.3)
Other	1 (3.1)
Sex	
Male	27 (84.4)
Duration of Dialysis (years)	
4.47 (4.3)	
Education Level	
1-12 years	16 (50.0)
Vocational/trade/some college	9 (28.1)
College or more	7 (21.9)
Employment Status	
Unemployed	3 (9.4)
Employed	7 (21.9)
Retired	22 (68.8)
Comorbidities	
Diabetes Mellius	15 (46.9)
Hypertension	32 (100)
Congestive heart failure	10 (31.3)
Coronary artery disease	8 (25.0)
Peripheral vascular disease	3 (9.4)
Stroke	4 (12.5)
Primary Cause of End-Stage Renal Disease	
Diabetes Mellitus	12 (37.5)
Hypertension	11 (34.4)
Glomerulonephritis	3 (9.4)
Other	6 (18.8)
Duration of Hemodialysis Session (hours)	3.8 (0.5)
Laboratory Values (average of baseline and 12 months)	
Hemoglobin (mg/dl)	10.8 (1.4)
Albumin (g/dl)	3.9 (0.4)
Kt/V	1.5 (0.2)
Dialytic Hemodynamics Over the 1-Year Period	
Change in pre- to postsystolic blood pressure (mmHg)	-9.9 (16.3)
Change in pre- to postdiastolic blood pressure (mmHg)	-3.3 (5.9)
Maximum decrease in systolic blood pressure (mmHg)	27.9 (10.2)
Maximum decrease in diastolic blood pressure (mmHg)	16.9 (5.4)
Average minimum systolic blood pressure (mmHg)	112.3 (13.3)
Average minimum diastolic blood pressure (mmHg)	60.6 (13.9)
Ultrafiltration rate (ml/kg/hour)	9.6 (2.8)

Laboratory values and dialytic hemodynamics are averaged over the 1-year period; the remaining characteristics are from baseline.

ize and provide further information on the relationship between intradialytic hemodynamics and changes in cognitive performance over time.

METHODS

Study Population

After approval from the Milwaukee VA Medical Center and Medical College of Wisconsin Institutional Review Board, we recruited patients >50 years of age who were receiving thrice weekly chronic HD at one of 3 Milwaukee area dialysis centers. We excluded patients with diagnosed dementia, Parkinson's disease, intracranial tumor or bleed within the previous 12 months, or traumatic brain injury. Additionally, we excluded patients who lacked stamina to undergo a 1-hour neuropsychological test battery. All participants provided written informed consent before beginning study procedures, and research was carried out according to the principles of the Declaration of Helsinki.

Data Collection Procedure

Participants completed a written survey regarding sociodemographics (eg, age, race, education, and employment status), duration of hemodialysis, and their personal history of hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, peripheral vascular disease, cirrhosis, and stroke. The presence or absence of comorbid conditions was confirmed using the medical record, and the primary cause of renal disease was obtained from the ESRD Registration Report. We collected hemoglobin and albumin values and a marker of dialysis adequacy (Kt/V) during the month of baseline and 12-month cognitive testing from the dialysis center medical records.

Two nephrologists obtained the ultrafiltration rate (UFR) and all sitting BP measurements (predialysis BP, dialytic BPs, and postdialysis BP) for 3 consecutive dialysis sessions at baseline and 3, 6, 9, and 12 months follow-up for a total of 15 sessions. These measurements are routinely collected every 15 to 20 minutes at our dialysis facilities. For each dialysis session, we calculated the minimum BP (lowest BP from any BP readings during dialysis, including pre- and postmeasurements), the maximum decrease in BP (predialysis BP minus the lowest BP for each dialysis session), and the change in BP from predialysis to postdialysis (predialysis BP minus the postdialysis BP) for both systolic (SBP) and diastolic BP (DBP), as well as the UFR (net amount of fluid [ml] removed divided by weight [kg] divided by the duration of dialysis [hours]). We then averaged each of these measures of intradialytic hemodynamics across all sessions for each patient.

Neurocognitive Testing

Trained study team members administered a battery of neurocognitive tests to each participant using standardized procedures. The battery assessed the following domains: executive functioning, memory, learning, language, and attention. The Montreal Cognitive Assessment (MoCA) was used to assess global cognitive functioning. The remainder of the neurocognitive battery included the Hopkin's Verbal Learning Test-Revised (HVLT-R), Trail Making Test A and B, Controlled Oral Word Association Test (COWAT), Animal Naming, and the Wechsler Adult Intelligence Scale-Fourth Edition Digit Span subtest. Cognitive domains assessed by each test are noted in the Results section. The Advanced Clinical Solutions Test of Premorbid Functioning also was included to estimate premor-

bid intelligence.[15] The Test of Premorbid Functioning accounts for age, gender, education level, self and parental occupation, religion, geographic area, and community environment both currently and during childhood. Cognitive testing was done after dialysis in 30 participants and prior to dialysis in 2 participants at baseline. Follow-up testing was completed on the same time schedule (postdialysis or predialysis) as the first testing session, except for 2 participants who changed from postdialysis to an off day for their convenience. On average, the neurocognitive battery took 40 minutes to complete. Published age, gender, education, and ethnicity corrected norms were used to score the neuropsychological tests.[16-19]

Table 2. Changes in Cognitive Test Scores From Baseline to 12 Months

Test (N)	Domain	Baseline	12 month	Change in Score	*P*-value[a]
MoCA Score (32)	Cognitive screen	21.8 (3.8)	21.7 (3.9)	-0.2(2.8)	0.84
Hopkin Verbal Learning					
Immediate (31)	Immediate memory	32.1 (9.8)	29.6 (8.2)	-2.5 (7.2)	0.27
Delayed (31)	Delayed memory	29.6 (10.9)	29.1 (9.7)	-0.5 (6.8)	0.86
Recognition (31)	Recognition memory	39.1 (14.1)	43.4 (12.2)	4.3 (13.4)	0.21
Trails A (30)	Simple attention, processing speed	40.6 (10.9)	43.9 (11.8)	3.3 (6.8)	0.27
Trails B (29)	Executive function, processing speed	39.5 (11.4)	42.9 (10.7)	3.4 (8.7)	0.26
COWAT (30)	Executive function, verbal fluency (phonemic), memory	43.1 (10.1)	41.1 (10.4)	-2.0 (7.0)	0.45
Animal Naming (30)	Executive function, verbal fluency (semantic), memory	46.4 (9.7)	46.7 (13.2)	0.3 (10.6)	0.93
Digit Span Total (31)	Working memory, attention	8.1 (2.7)	8.1 (2.5)	0.0(1.8)	1.00

[a]*P*-value comparing baseline to 12-month scores based on *t*-test.
Abbreviations: MoCA, Montreal Cognitive Assessment; COWAT, Controlled Oral Word Association Test.

Statistical Analysis

We calculated characteristics of the participants as means (SD) for continuous measures and frequencies for categorical data. Cognitive test scores at baseline and at 12-month follow-up were calculated with standard methods, then subtracted to yield the outcome variables – change in cognitive function. We compared the scores of the cohort at baseline and 12 months using *t*-tests. Based on our initial finding of little change in cognitive test scores over 1 year for the full cohort, we also evaluated participants with less than 1 year of dialysis separately. We tested the association between BP fluctuation and change in cognitive test scores by linear regression. Our analysis centered on SBP as it has shown to be a predictor of clinical outcomes in people over 50 years.[20]

Due to the exploratory nature of the study, we did evaluate the association of each hemodynamic variable with the change in each cognitive test score in parallel analyses. A Benjamini-Hochberg false discovery rate adjustment was used to account for significance testing of 36 associations. If the association between a measure of BP fluctuation and a measure of change in cognition was significant (adjusted *P*-value <0.05) in a simple linear regression analysis, the association was then tested in a multivariable regression model that adjusted for age, race (ie, white or not), presence of diabetes, and hemoglobin level (average of baseline and 12 months). We chose covariates based on prior work demonstrating an association with cognitive function in the dialysis population.[3,14] SAS V 9.2 (SAS Institute Inc, Cary, North Carolina) was used for the statistical analysis.

RESULTS

Demographic and Clinical Characteristics

Thirty-nine participants completed the baseline testing and 32 completed the 1-year follow-up testing. Of the 7 participants who did not complete follow-up testing, one relocated, three died, one transferred to peritoneal dialysis, one underwent treatment for lymphoma complicated by infection and delirium (an exclusion criteria), and one declined follow-up testing due to inconvenience. The mean (SD) age of the 32 participants who completed the follow-up testing was 66.8 (10.0) years, and diabetes mellitus and hypertension were present in 47% and 100% of participants, respectively (Table 1).

Intradialytic Hemodynamics

The mean intradialytic SBP ranged from 94 mmHg to 165 mmHg (mean [SD] 133.3 [16.5]). The mean maximum intradialytic SBP ranged from 127mmHg to 198 mmHg (mean [SD] 167.6 [18.8]). See Table 1 for the mean and SD of each measure of BP fluctuation and the UFR for our cohort. BP fluctuation among participants who dropped out was not statistically different from fluctuation among those who completed the study (data not shown).

Cognitive Outcomes for Full Cohort

Overall, a high degree of cognitive impairment was observed at baseline, with almost 60% of the cohort scoring 2 SDs below the population mean on the screening measure of global cognitive function (MoCA).[14] The Test of Premorbid Functioning score (mean [SD]) was not statistically different from the predicted score (87.3 [10.6] vs 91.7[8.9], *P*=0.08), indicating that our cohort's observed impairment reflected a decline from premorbid functioning. Mean test scores for our cohort did not change significantly from baseline to follow-up (Table 2). There was no significant decline in any of the cognitive scores from baseline to follow-up. Indeed, in some cases, there was nonsignificant improvement. To further explore our data, we then examined the

Table 3. Comparison of the Change in Cognitive Test Scores for Participants With <1 Year of Dialysis at the Start of the Study to Participants With ≥1 Year of Dialysis

	Change in Score (SD) for Participants With <1 Year of Dialysis (N=9)	Change in Score (SD) for Participants With ≥1 Year of Dialysis (N=23)
MoCA score	-0.6 (2.9)	0.0 (2.8)
Immediate norm	-5.2 (8.4)	-1.5 (6.5)
Delayed norm	-0.8 (7.8)	-0.3 (6.6)
Recognition norm	4.8 (11.7)	4.0 (14.3)
Trails A norm	1.1 (4.6)	4.2 (7.5)
Trails B norm	1.3 (7.5)	4.4 (9.3)
COWAT norm	-2.3 (8.1)	-1.9 (6.8)
Animal Naming *t*-score	3.2 (11.5)	-1.1 (10.1)
Digit Span Total norm	0.1 (1.9)	0.0 (1.8)

Abbreviaions: MoCA, Montreal Cognitive Assessment; COWAT, Controlled Oral Word Association Test.
Laboratory values and dialytic hemodynamics are averaged over the 1-year period; the remaining characteristics are from baseline.

9 participants who we enrolled within 1 year of starting HD. In those patients there was a more uniform tendency of cognitive scores decrease. Specifically, for the cognitive tests that did have a decrease in score from baseline, the mean change (SD) in MoCA was -0.6 (2.9) vs 0.0 (2.8), in Hopkins Immediate memory was -5.2 (8.4) vs -1.5 (6.5), in Hopkins Delayed memory was -0.8 (7.8) vs -0.3 (6.6), and in COWAT -2.3 (8.1) vs -1.9 (6.8) for the 9 participants vs the remaining 23 participants, respectively (Table 3). None of these comparisons were significant.

Relationship Between Intradialytic Hemodynamics and Cognitive Outcomes

There was no significant association between intradialytic BP variables and changes in cognitive test scores in univariable analysis. However, a higher UFR was associated with improvement in performance on Trails B (a test of executive functioning) in both bivariate (Table 4) and multivariable analysis. In the multivariable analysis every 1 ml/kg/hr increase in UFR was associated with 2.4-point positive change in Trails B score over the study year ($P<0.01$). This association persisted after we adjusted for Kt/V in our model.

DISCUSSION

Contrary to our hypothesis that cognitive decline in the dialysis population is mediated by intradialytic hemodynamic fluctuation, we found no association between intradialytic BP variability and changes in cognitive performance. Moreover, we found that higher average UFR, a surrogate for rapid fluid removal, was associated with improvement rather than deterioration in performance on Trails B, a test of executive functioning. Finally, we did not see the expected drop in cognitive status over the study period.

Although it has been postulated that hemodynamic fluctuations during dialysis may contribute to cognitive dysfunction,[1,8,10,21] ours is the first longitudinal analysis to directly address the relationship between hemodynamics during dialysis and long-term changes in cognitive status. Previous evaluations of the impact of intradialytic hemodynamics on cognitive performance are limited to cross-sectional analyses, which cannot account for the impact of prior hemodynamic fluctuations on cognitive impairment.[14,22,23] In a cross sectional analysis of the Frequent Hemodialysis Network Trial (FHNT) that evaluated correlates of cognitive impairment, investigators did not find that hemodynamic variables of predialysis BP or need for intravenous saline for hypotension during dialysis were associated with cognitive impairment.[23] Additionally, in the FHNT, the ultrafiltration volume (in ml/kg) was not associated with a Trails B score; however, this study used a cutoff score to designate impairment in Trails B and did not adjust the ultrafiltration volume for duration of dialysis session, which may have limited their findings. Our finding that higher UFR was associated with improved scores on Trails B at 1-year follow-up warrants further investigation to determine if this is a statistical finding or a true clinical association.

A possible explanation for the association between higher UFR and improvement on Trails B is that the higher ultrafiltration per session led to an increase in middle molecule clearance, which we did not measure in our study. Middle molecule clearance need further evaluation in cognitive function, especially as they are postulated to be neurotoxic.[1] Of note, Kt/V is more of a measure of small molecule clearance and was not associated with Trails B score in our study or previous literature.[24]

In contrast to our results, there is literature that suggests a role of intradialytic BP variability in cognitive impairment. In a study evaluating changes in cognitive performance from predialysis to postdialysis, the frequency of hypotensive episodes (SBP <90 or DBP <50) during dialysis was associated with decline in performance on tasks of attention.[25] However, it was not demonstrated whether the cognitive impairment noted after a dialysis session is a permanent versus a temporary effect. In a randomized trial evaluating intradialytic hemodynamic stress, investigators demonstrated that, over a 1-year period, persons dialyzed with cooled dialysate had better stability of mean arterial pressures during dialysis and no changes in brain white matter microstructure, whereas the control group exhibited increased variability in mean arterial pressures and a decrease in white matter integrity.[26] However, they did not report cognitive performance results, which have greater patient relevance.

The lack of overall cognitive decline over our 1-year study period also is surprising as a previous study noted a decrease in global cognitive score in a hemodialysis cohort over a 1-year period,[6] and there is strong evidence demonstrating the high prevalence of cognitive impairment in the HD population.[27] However, there is no clear evidence on the timing of cognitive decline in relationship to dialysis initiation. Literature demonstrates that the incidence of stroke is actually highest in the 2 months surrounding dialysis initiation, with incidence rates back to baseline at 1 year after initiation.[28] If cognitive impairment results from a

Table 4. Change in Test Scores (12 Month Score Minus Baseline Score) Associated With Change in Each SBP and UFR Variable

Cognitive Tests	Systolic Blood Pressure Measure	Rate of Change in Difference of Score[a] From Baseline to 12 Months	95% CI	*P*-value	Corrected *P*-value[b]
Montreal Cognitive Assessment (MoCA)	Change in blood pressure pre to post	-0.07	-0.71, 0.57	0.81	
	Maximum decrease in blood pressure	-0.15	-1.00, 0.70	0.71	
	Minimum blood pressure	-0.01	-0.80, 0.77	0.97	
	Ultrafiltration rate	0.01	-0.36, 0.38	0.95	
Hopkins Immediate	Change in blood pressure pre to post	1.25	-0.91, 3.42	0.25	
	Maximum decrease in blood pressure	0.66	-1.74, 3.05	0.58	
	Minimum blood pressure	-1.69	-3.62, 0.23	0.08	0.46
	Ultrafiltration rate	-0.24	-1.21, 0.73	0.62	
Hopkins Delayed	Change in blood pressure pre to post	-1.31	-3.35, 0.73	0.20	
	Maximum decrease in blood pressure	2.32	0.21, 4.43	0.03	0.30
	Minimum blood pressure	-0.45	-2.37, 1.47	0.63	
	Ultrafiltration rate	-0.28	-1.20, 0.64	0.54	
Hopkins Recognition	Change in blood pressure pre to post	2.75	-1.26, 6.77	0.17	
	Maximum decrease in blood pressure	-1.04	-5.54, 3.45	0.64	
	Minimum blood pressure	-2.46	-6.15, 1.22	0.18	
	Ultrafiltration rate	-0.04	-1.86, 1.79	0.97	
Trails A	Change in blood pressure pre to post	-0.19	-2.31, 1.93	0.86	
	Maximum decrease in blood pressure	-0.37	-2.69, 1.95	0.75	
	Minimum blood pressure	-0.67	-2.60, 1.27	0.49	
	Ultrafiltration rate	0.51	-0.41, 1.43	0.26	
Trails B	Change in blood pressure pre to post	-2.32	-4.92, 0.29	0.08	0.46
	Maximum decrease in blood pressure	1.55	-1.39, 4.49	0.29	
	Minimum blood pressure	0.06	-2.47, 2.59	0.96	
	Ultrafiltration rate	1.95	0.91, 3.00	<0.01	0.03
Controlled Oral Word Association Test (COWAT)	Change in blood pressure pre to post	1.05	-1.10, 3.21	0.33	
	Maximum decrease in blood pressure	-0.50	-2.87, 1.88	0.67	
	Minimum blood pressure	-1.33	-3.26, 0.60	0.17	
	Ultrafiltration rate	0.58	-0.43, 1.59	0.25	
Animal Naming	Change in blood pressure pre to post	0.36	-0.86, 1.58	0.55	
	Maximum decrease in blood pressure	0.00	-1.36, 1.37	1.00	
	Minimum blood pressure	-0.36	-1.49, 0.77	0.52	
	Ultrafiltration rate	0.26	-0.29, 0.82	0.34	
Digit Span	Change in blood pressure pre to post	-0.11	-0.67, 0.46	0.70	
	Maximum decrease in blood pressure	0.22	-0.39, 0.83	0.46	
	Minimum blood pressure	-0.55	-1.02, -0.08	0.02	0.30
	Ultrafiltration rate	0.06	-1.87, 3.06	0.62	

[a]Rate of change in score per 10 mmHg increment in systolic blood pressure measures and 1 ml/kg/h for ultrafiltration rate.
[b]Corrected *P*-value adjusts for false positive results present in multiple comparison testing.

mechanism similar to stroke (ie, reduced cerebral perfusion and ischemic injury),[29] then our use of prevalent patients with an average of 4.5 years on dialysis may not have been able to capture hemodynamic associated cognitive decline. Our evaluation of the 9 participants with less than 1 year of dialysis at enrollment did show a trend toward greater decline in cognitive test score compared to those who had been on dialysis for more than 1 year. We hypothesize that cognitive decline associated with intradialytic hemodynamic instability may occur early after dialysis initiation when patients are still adjusting to the dialysis process.

We acknowledge several limitations. First, small sample size (with only 32 participants completing the study) limits interpretation of our results, as we were not able to obtain our goal sample size of 43 participants. Additionally, the majority of participants in our small cohort were African American, which is in contrast to most literature in this field with predominantly white participants. Race is associated with performance on cognitive testing.[30] It is important to note that our cohort is representative of the Milwaukee-area dialysis population and demonstrates similar levels of cognitive impairment seen in other studies.[6,27] Second, we observed severe cognitive impairment at baseline with mean (SD) MoCA score of 21.8 (3.8). This may have limited our ability to detect further decline in performance due to floor effects as we did not note further decline over the 1-year period. Third,

with an average minimum intradialytic SBP of 112 mmHg, our cohort did not demonstrate a high degree of hypotension; thus our cohort may not have been at high risk for hypotensive-related ischemic brain injury as a cause of cognitive decline. Fourth, our use of changes in sphygmomanometer-measured BP may not have been adequate to detect hemodynamic instability. In the above-mentioned study that demonstrated an association between intradialytic hemodynamic stability and preserved brain white matter integrity, the investigators used a novel hemodynamic model that used beat-to-beat measurements and variability, which provides greater granularity of intradialytic hemodynamics compared to sphygmomanometer-measured BP changes. Finally, we did not obtain information on use of interventions to avoid hypotension such as saline infusion or dialysate cooling.

CONCLUSIONS

Our pilot study is the first longitudinal evaluation of cognitive changes in relation to intradialytic hemodynamics that included a comprehensive evaluation of intradialytic BPs, UFR, and cognitive domains. The contribution of dialysis to cognitive decline is an important area for research. Our study does not demonstrate that intradialytic BP fluctuations are associated with change in cognitive test scores in prevalent dialysis patients over a 1-year period. However, higher ultrafiltration rate was associated with improved executive functioning. The role of both hemodynamics and ultrafiltration in cognitive impairment needs further investigation in larger cohorts with a more sensitive measure of hemodynamics and cerebral perfusion. Such an association may be more apparent at the time dialysis is initiated, when cognitive changes may be more likely. This is an important area of focus as both intradialytic BPs and ultrafiltration rate are potentially modifiable through use of medications, changes in dialysate temperature, session duration, and dialysis modality.

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