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To Explore the Correlation between the Severity of Chronic Kidney Disease and the Hemodynamics of Small Cerebral Vessels under Transcranial Color Doppler

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Abstract: *The purpose of this study is to investigate the correlation and its clinical value between the severity of chronic kidney disease and cerebral arterial blood flow dynamics by transcranial color-coded duplex sonography (TCCD). We collected patients with cerebral small vessel disease with chronic kidney disease (CKD) who visited Hongqi Hospital affiliated with Mudanjiang Medical University, gathered between October 2020 and December 2021. The results were analyzed and then divided into 3 groups according to different stages of CKD: 73 patients in CKD stage I-III, CKD-IV, and CKD-V.Those with stable serum creatinine and small cerebral vascular lesions without stenosis or occlusion of intracranial large vessels were examined by TCCD. The spectrum data of intracranial great vessels of the three groups were measured and the vascular resistance index (RI) and pulsatility index (PI) were calculated. The obtained data were analyzed statistically. Finally, it is concluded that: ①There was no significant difference in general data (gender and age) among the 3 groups (p>0.05); ②There was no statistically significant difference between the bilateral anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) RI and PI values in the three groups (p>0.05).③There were no significant differences in ACA-PI and PCA-PI values among the three groups (p > 0.05). Each of the three groups' MCA-PI levels corresponded to a different stage of CKD in the patients. Patients with stage V CKD had PI levels that were noticeably greater than those of patients with stages I–III and IV. ④At various stages of CKD, there was a linear relationship between the MCA-PI value and serum creatinine level; also, the MCA-PI value increased linearly as the serum creatinine level increased. To sum up, TCCD has certain clinical application value for stroke risk assessment in CKD patients with small cerebral vessel diseases. It can capture the small cerebral blood flow changes in CKD patients at an early stage, non-invasive assessment of potential stroke probability in CKD patients, and help clinical physicians intervene early to lower the incidence and death of cerebrovascular disorders in patients with chronic kidney disease.*

Keywords: *Transcranial Color-Coded Duplex Sonography; Chronic Kidney Disease; Small Cerebral Vascular Disease*

1. Introduction

Recently, the nephron-brain axis has gained more attention due to the anatomical and functional similarities between the two organs that increase susceptibility to vascular risk factors such as high flow/low vascular resistance and local autoregulation[1]. It is now understood that CKD is a disease that affects the entire body and involves the central nervous system[2]. Studies have found that CKD affects large, medium, and small blood vessels throughout the body, and also affects the structure of the brain. Underlying conditions that cause CKD, such as diabetes or high blood pressure, can also have an impact on the patient's vascular system throughout the body. CKD accelerates atherosclerosis without dialysis and often results in mid-level calcification[3-4]. Even in mild-to-moderate CKD patients, decreased

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glomerular filtration rate (GFR) leads to arterial thickening, increased arterial stiffness, and increased wall shear stress [5]. CKD not only changes brain structure but also affects brain function. CKD can lead to cognitive impairment in patients, but its pathophysiology is very complex, and the "vascular hypothesis" suggests that impaired cerebral hemodynamics in CKD may lead to cognitive decline[6]. Stroke prevention strategies for patients with CKD are mostly comparable to those for individuals with normal renal function, even though CKD independently raises the risk of stroke and the burden of ischemic small vessel disease. In addition, CKD patients have corresponding concurrent diseases before dialysis, but most current studies focus on the hemodynamics of dialysis patients, and little is known about the changes in cerebral blood flow in patients before dialysis[7-8]. Currently, ultrasound is the primary method used to measure cerebral hemodynamic parameters, while vascular structure is the primary method used to measure other imaging metrics. A reliable and non-invasive bedside tool for assessing cerebral hemodynamics, such as distal vascular blood flow resistance, is TCCD[9-12]. Therefore, this study aims to analyze and compare whether cerebrovascular lesions by TCCD technology accompany differences in cerebrovascular hemodynamics in patients with different stages of pre-dialysis CKD, to assist clinicians in evaluating cerebral blood flow in pre-dialysis CKD patients and provide certain clinical references for improving the prognosis of patients with chronic kidney disease accompanied by cerebrovascular lesions.

2. Material and Methods

2.1. Patients

Patients with CKD accompanied by stroke and no dialysis who came to our hospital from October 2020 to December 2021 at different periods were selected. eGFR was calculated according to the Collaborative equation for the Epidemiology of Chronic Kidney Disease.

$$eGFR=175\times[\text{serum creatinine}]-1.154\times \text{age} -0.203(\times 0.742, \text{if female}) \quad (1)$$

CKD patients were staged according to the 2012 KDIGO Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease: Stage I: Slight changes in renal function, estimated GFR ≥90mL/min; Stage II: mild, estimated GFR 60-90 ml /min; Stage III: moderate, GFR estimated at 30-60mL/min; Stage IV: Severe, estimated GFR 15-30mL/min; Stage V: Renal failure with an estimated GFR < 15ml/min. The ethical committee of the hospital approved the trial, and before its performance, patients were informed and provided their signed consent. The inclusion criteria:(1)Patients with small cerebral vessel lesions confirmed by CT or MRI; (2)Blood pressure values of less than 150mmHg systolic and less than 90mmHg diastolic should be controlled by drugs; (3)If type II diabetes is identified, following the Chinese Guidelines for the Prevention and Treatment of Type II Diabetes (2020 Edition), treatment should be initiated, the postprandial blood glucose should be controlled below 10mmol/L; (4)All patients were diagnosed with CKD according to the KDIGO Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease (2012 edition).The exclusion criteria : (1)Patients with acute renal impairment; (2)Patients with carotid artery stenosis rate of more than 50% accompanied by unstable plaque; (3)Patients with intracranial large blood vessel stenosis or occlusion; (4)poor temporal window display; (5)Patients with open intracranial collateral circulation caused by clinical medication.

2.2. TCCD

A Philips EPIQ 7C machine (Philips Healthcare, Best, The Netherlands) was used in our study.TCCD was performed using the X5-1 probe(1~5MHz) with color doppler flow imaging(CDFI)function and pulsed-wave doppler (PW) function. X5-1 probe was selected, the examination condition was adjusted to TCD mode, the patient was asked to take the supine or lateral position, the head was tilted to the opposite side, the target temporal bone was exposed, and the probe was placed above the zygomatic arch on both sides. The temporal window between the outer corner of the eye and the external ear canal gives it a good two-dimensional section. Firstly, the standard horizontal cross-section of the midbrain was displayed in the two-dimensional section. After adjusting the direction of the probe and the size and position of the color Doppler sampling frame, the complete and clear basilar artery blood flow image was displayed, a better color blood flow map was obtained under the guidance of the color blood flow, the direction, trend, and color of the blood flow were observed, the area of interest was selected according to the needs, and the spectral doppler sampling volume and sampling angle were adjusted to scan ACA,

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MCA, and PCA. The corresponding spectrum waveform and parameters were obtained, and the PI values of ACA, MCA, and PCA were automatically calculated and recorded by the system software. Finally, the RI and PI values of ACA, MCA, and PCA on the left and right sides of the three groups were compared, and whether there were differences in RI and PI values of ACA, MCA, and PCA among the three groups; If there were differences in blood vessel observation indicators, the correlation between them and blood creatinine level was further analyzed.

2.3. Statistical analysis

The acquired data were statistically processed using SPSS 26.0 statistical software. The measurement data were expressed as mean ± standard deviation($\bar{x}$ ±S), median, and quartile, and inter-group comparison was performed by two-sample T-test and independent-samples T-test. Independent sample Kruskal-Wallis test (subject to normal distribution) and analysis of variance (not subject to normal distribution) were used for multi-group comparison. The value of TDD-PI in vascular distribution was used as the dependent variable, and the PI value and serum creatinine level were analyzed by linear regression with one variable. $p < 0.05$ was considered statistically significant.

3. Results

A whole group of 73 participants were included in it, ranging in age from 26 to 78 years, with a mean serum creatinine level of 301.74±117.64 (μmol/L). According to the CKD stage, the patients were divided into 3 groups, including 24 patients in stage I-III, 25 patients in stage IV, and 24 patients in stage V. The feasibility of the study was indicated by the comparison of general data (gender and age) among the three groups, which revealed no statistical significance ($P > 0.05$), indicating the feasibility of the study (Table 1).

Table 1: Information on research objects.

CKD group	Number	Age	Sex(male:female)
I-III	24	54.97±10.61	14:10
IV	25	56.21±11.40	13:12
V	24	55.97±11.59	9:15

The general information of the two groups was compared ($p > 0.05$).

After the independent-samples T-test, the left and right ACA-PI values (p=0.622), the left and right MCM-PI values (p=0.842), and the left and right PCA-PI values (p=0.386) of the three groups were compared, and the results showed not any statistically significant variations between the groups. (Table 2).

Table 2: Comparison of RI and PI values of ACA, MCA, and PCA on both sides ($\bar{x}$ ±S).

Group	Left	Right	*t*	*p*
ACA-PI	0.82±0.11	0.80±0.13	0.670	0.622
MCA-PI	1.03±0.18	1.00±0.17	0.970	0.842
PCA-PI	0.87±0.16	0.91±0.17	0.803	0.386

The PCA-PI values of each of the three groups were examined using the analysis of variance and showed no statistically significant variations between the groups. (Table 3).

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Table 3: Comparison of ACA-PI values between the three groups ($\bar{x}$ ±S).

CKD Group	Number of vessels	ACA-PI	F	*p*
I-III	12	0.74±0.12	2.982	0.061
IV	30	0.83±0.12		
V	7	0.86±0.08		

Inter-group analysis of MCA-PI values of the 3 groups was conducted by non-parametric independent sample test, and pairwise comparison among the three groups showed that there were statistically significant differences between CKD stage I-III vs CKD stage V, CKD stage IV vs CKD stage V, and the PI value of patients with CKD stage V was significantly higher than that of patients with stage I-III and stage IV (Figure 1, Table 4, Table 5, and Figure 2).

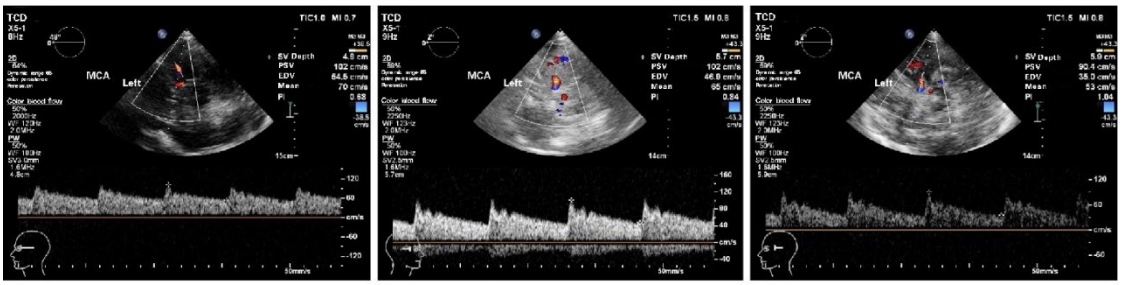

Figure 1: Detection of MCA-PI values of patients in 3 groups

Table 4: Comparison of MCA-PI values among the three groups.

CKD Group	Number of vessels	Median (*P*25,*P*75)	Rank sum test	
			H	*p*
I-III	33	0.93(0.84,1.07)	27.750	0.000
IV	55	0.97(0.91,1.05)		
V	34	1.23(1.06,1.27)		

Table 5: Comparison of MCA-PI values in pairs among the three groups.

Group	H	*p*
I-III—IV	-9.009	0.741
I-III—V	-43.001	0.000
IV—V	-33.992	0.000

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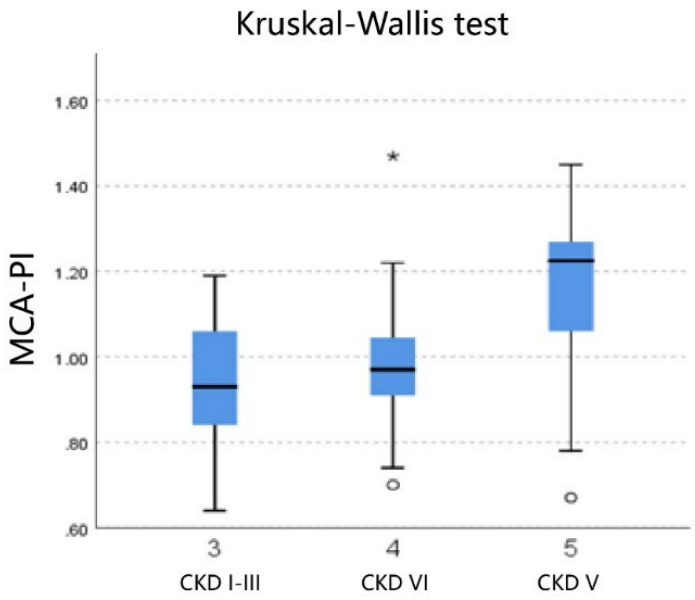

Figure 2: Comparison of MCA-PI values among the three groups.

The analysis of variance was used to analyze the PCA-PI values of the three groups, and the differences among the groups were not statistically significant (Table 6).

Table 6: Comparison of PCA-PI values in the three groups ($\bar{x}$ ±S).

CKD group	Number of vessels	PCA-PI	F	*p*
I-III	15	0.86±0.15	0.823	0.444
IV	36	0.88±0.16		
V	13	0.93±0.17		

Finally, the MCA-PI value and serum creatinine level of patients in the 3 groups were included in linear regression analysis, and the results showed that the serum creatinine concentration of patients was significantly correlated with MCA-PI ($P < 0.05$), and was positively correlated(Figure 3 and Table 7).

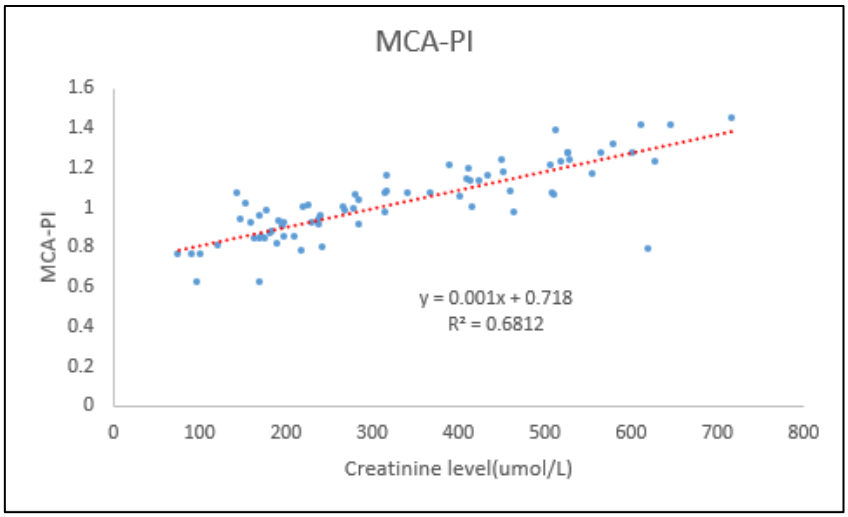

Figure 3: Scatterplot of MAC-PI values and creatinine levels.

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Table 7: Linear regression analysis of MCA-PI values and creatinine levels.

Coefficient a						
Model		unstandardized coefficient		Standardization coefficient	t	P
		B	Standard error	Beta		
	(Constant)	0.718	0.042		17.243	0.000
	creatinine	0.001	0.000	0.704	8.059	0.000
a. Dependent variable: MCA-PI value						

MCA-$\hat{PI}$ =0.718+0.001* serum creatinine.

4. Discussion

In the past 50 years, nephrologists have been focusing on the treatment and prevention of the high incidence and mortality of cardiovascular diseases in patients with CKD [13], but in fact, the incidence of cerebrovascular diseases is generally high in all stages of CKD. It might indicate a synergistic effect of several risk factors, including diabetes, hypertension, and atherosclerosis [14-16]. In this study, CKD patients with cerebral small vessel disease were selected and grouped according to CKD classification, and intracranial cerebral hemodynamics were examined by TCCD. There was no statistical difference between ACA-PI and PCA-PI groups (P=0.061; P=0.444), and there are differences in MCA hemodynamics in patients with CKD at different stages, and the PI value of patients with CKD stage V is significantly higher than that of patients with CKD stage I-III and IV, which is similar to the results obtained by Ghoshal S et al[17] through TCD. Higher distal intracranial resistance and a markedly increased ischemic small-vessel disease load in the anterior cerebral circulation are found in patients with CKD stage III or above. The current retrospective study on cerebral hemodynamics in patients with CKD explains this result by suggesting that CKD can promote endothelial dysfunction, which can result in remodeling and hardening of the great arteries due to vascular calcification, inflammation, and disorders of nitric oxide metabolism. Therefore, kidney function is an independent determinant of remodeling and hardening of carotid arteries and aorta, while MCA is the main intracranial branch of the internal carotid artery. Its course is relatively fixed and there are few congenital variations, so the primary way that CKD alters cerebral hemodynamics is by raising MCA's distal blood flow resistance. Therefore, it is found that currently, intracranial artery lesions in Chinese patients mostly occur in MCA[18], but are not significantly manifested in ACA. Therefore, early recognition and intervention of MCA sclerosis and regular follow-up observation of MCA hemodynamics are of great significance for preventing cerebrovascular diseases and improving prognosis in CKD patients. In addition, this study also concluded that a significant connection was observed between the serum creatinine concentration and MCA-PI, that is, the MCA-PI value of the patient increased with the increase of the serum creatinine concentration, indicating that the level of cerebral atherosclerosis would become higher with the development of the disease course. Based on serum creatinine levels, eGFR in the Rotterdam trial was independently linked to a decrease in the Rotterdam study; Cerebral blood flow decreased by 0.42mL/min/100mL(95%CI 0.01-0.83) for every 1 standard deviation decrease in eGFR [19]. In addition, more and more evidence shows that the relationship between renal function impairment and cerebrovascular diseases is mediated by vascular mechanisms. For example, Seliger et al [20] proved that higher serum creatinine concentration is associated with vascular dementia, indicating that renal function impairment is associated with an increased risk of cerebral atherosclerosis and stroke as a determinant of vascular dementia. Therefore, active intervention in the course of CKD and control of serum creatinine levels in the early clinical stage can slow down or even avoid the occurrence of cerebrovascular complications. Moreover, by monitoring the change of MCA-PI value in CKD patients, the effectiveness of clinical intervention in CKD can be effectively judged.

There are still some limitations in this study: (1)The patients were relatively old (mean age 55), and

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there was a lack of other medical history data, such as blood lipid indexes, smoking history, nephrogenic heart disease, and coronary heart disease history, and other possible confounding factors could not be excluded. (2)Because hemodynamic changes may occur in the acute phase after stroke, the TCCD data obtained within 72 hours after stroke and the TCCD data with open collateral were not included in this study, so the sample size was relatively small and there was a certain sampling error. (3)This study was limited to patients with small cerebral vessel lesions, so it could not evaluate the influence of family hereditary or concurrent medical complications on cerebrovascular PI value. Moreover, the patients in this study were all small cerebral vessel diseases and other cerebrovascular lesions were not comprehensively evaluated.

In summary, the study's findings demonstrated that MCA hemodynamics were different in patients with CKD at different stages. Patients with CKD stage V had a considerably higher PI value than patients with CKD stages I-III and IV, and there was a linear positive correlation found between the MCA-PI value and blood creatinine level. With the increase in serum creatinine level, the MCA-PI value increased. As a result, TCCD can help with clinical early intervention, monitor changes in cerebral arterial blood flow dynamics in patients with CKD who have small cerebral vessels, identify small cerebral blood flow changes in CKD patients early on, and lower the incidence and mortality of cerebrovascular diseases in those with CKD.

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