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The cardiovascular mononeuropathy in Hemodialysis Patients analysed by a combination with reactivity tests to noninvasively evaluate skin sympathetic nerve activity and skin microvascular function by (LDF)

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Abstract

Aim: Although several patients with kidney disease have simultaneous dysfunction of the parasympathetic and sympathetic nervous systems, orthostatic hypotension during a hemodialysis (HD) procedure impacts not only the form of treatment but overall comfort of life for patients with HD. Despite a number of methods that are not invasive and have already been used to assess autonomous functioning, a system for monitoring malfunction throughout filtration of blood therapy which has yet to be discovered.

Methods: Regarding the purpose of monitoring the autonomous function of stable 40 regular HD patients and 35 healthy controls, we examined the clinical application of the laser-Doppler blood flow meter (LDF). By detecting the periflux blood flow decreasing velocity (PDV) while combined with the Valsalva manoeuvre, the LDF device which was used for an autonomous test. We also looked at the relationship between PDV and traditional atherosclerosis testing.

Results: The baseline PDV (5.30 ± 2.93), comparative to subjects who were in excellent condition (9.65 ± 7.10), was substantially decreased in the HD populace. Furthermore, we discovered a substantial connection between PDV and established parameters like heart rate fluctuation and ankle-brachial blood pressure indexing.

Conclusion: Regarding assessing autonomous functioning in hemodialysis patients, evaluation of PDV by LDF is just as effective as the standard approach. The benefit from regular and recurring assessments of autonomous dysfunction is made possible by the device's ease.

Keywords: Parasympathetic; Sympathetic; Hemodialysis; ABI; PWV; Autonomous neuropathy; Periflux blood flow; Laser-Doppler blood flowmeter; Orthostatic hypotension

1. Introduction

A major factor of mortality in hemodialysis (HD) patients is cardiovascular diseases, which may be explained in part by anomalies in cardiovascular autonomous control.

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The prevalence of autonomous abnormalities in the HD population is being influenced by an increase in the proportion of individuals with HD who are older and have diabetes mellitus (DM). Cardiovascular disease (CVD) is a highly common complication and the first cause of death in patients with end-stage renal disease (ESRD) on haemodialysis (HD). In this population, mortality due to CVD is 20 times higher than in the general population and the majority of maintenance HD patients have CVD. (1). Orthostatic hypotension frequently has an impact on HD patients' everyday quality of life in addition to the modalities during and after HD sessions (2). The condition has been linked to decreased heart function brought on by left ventricular hypertrophy and myocardial interstitial fibrosis (3). Another explanation for this problem is autonomous neuropathy, which is brought on by uremic baroreceptor toxicity (4). Numerous studies have found that HD patients with intra- or post-dialysis hypotension have impaired heart baroreceptor sensitivity (5, 6). According to Converse et al., one significant factor contributing to hypotension during HD sessions is the sudden removal of reflex vasoconstriction (7). The Valsalva manoeuvre, the response to orthostasis, and the measurement of the coefficient of variation of R-R intervals (CVRR) are common tests of the parasympathetic nervous system's integrity (8). When compared to the general population, the Valsalva ratio and heart rate responses were both decreased in the HD or peritoneal dialysis group (6, 9).

These findings point to a combination of sympathetic and parasympathetic nervous system dysfunction in uremic situations. Although the pathophysiology is yet unknown, cardiovascular autonomic dysfunction is intimately associated to the morphological and distinguishing changes of cardiovascular arteries (10–12). Although numerous non-invasive techniques, including thermography, pulse-wave velocity, and ankle-brachial blood pressure index (ABI), have been used to assess peripheral artery disorders (PAD), no monitor has been developed for blood purifying therapy. For the purpose of analyzing blood flow during blood purification therapy, the non-invasive continuous monitoring method (NICOMM) of a micro-circulation monitor employing a laser-Doppler blood flowmeter (LDF) was carried out (13). Additionally, the LDF device can be used for autonomic tests, in which subjects are just required to undergo periflux blood flow monitoring and the Valsalva manoeuvre, rather than exercise or undergo invasive research. Due to the extremely low amount of load in each trial, the device is anticipated to be beneficial for measuring autonomic function in HD patients before or after a dialysis session. We enlisted HD patients with stable dialysis therapy and without diabetes because inadequate dialysis and DM could aggravate autonomic dysfunction, which can be caused by atherosclerosis in the HD population. This study's initial objective was to assess LDF's usefulness for assessing autonomic function in patients with typical HD. The second objective was to demonstrate that blood flow monitoring by NICOMM suggests the severity of atherosclerosis in order to assess the relationship between LDF levels and traditional tests. We also looked at whether LDF levels could be restored in HD patients by using an anti-platelet medication that is widely used to treat PAD.

2. Patients and Methods

The study included 40 healthy volunteers (20 females and 20 males) and 34 stable HD patients (17 females and 17 males). Each participant provided written, full agreement to participate in the study. Chronic glomerulonephritis or renal sclerosis were the causes of renal failure. Because many of the patients with DM-induced renal failure have variable degrees of autonomic dysfunction, they were not included in the study. HD patients had been receiving highly stable HD therapy for more than 3 months prior to the measurement, and they had been undergoing dialysis using the same membrane and method throughout the study. All of the subjects chosen for this study met the definition of hemodynamic stability, which was defined as the absence of episodes of hypotension during the previous three months with three weekly HD sessions (14). Three times a week, maintenance HD was performed for three to four hours each time, using blood flow rates of 150 to 220 mL/min and dialyses flow rates of 500 mL/min with Na+, K+, Cl-, Ca2+, Mg2+, HCO3-, and CH3COO- concentrations of 140, 2, 0, 110, 3, 0, and 1, respectively.

The test was conducted either early in the morning or late in the afternoon, and each individual was asked to abstain from caffeine and smoking for at least 12 hours beforehand. Prior to the trial, participants stopped taking aspirin and other NSAIDs for a week. During the course of the trial, hypotensive medications like angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and b-blockers remained steady. 30 patients took these medications in the hypertension (HT) group and 7 in the non-hypertensive (non-HT) group.

2.1. Laser-Doppler Flowmeter

25 ± 2°C was the temperature in the room. An earlobe and a finger without an arteriovenous fistula were both carefully washed with ethanol and then left to dry for the 40-min adaptability period. A LDF, CyberMedR CDF-2000, with a 800 mm wavelength, was linked to these locations to assess the microvascular blood flow (Fig. 1A). The laser irradiator and detector can be installed together in the compact probe section of the innovative LDF probe due to its unique size. Illuminator and detector are not housed inside the same probe in a traditional LDF probe. Because of the significant

noise caused by body movement, the traditional probe is not appropriate for a long-term measurement. However, the Illuminator and detector are placed at the integrated probe's point of operation to reduce noise and enable extended measurement (13–15). Double-sided tape was used to secure the LDF probe to a finger or earlobe while the individuals were seated.

2.2. Analyzing Autonomous Motion during the Valsalva Manoeuvre

The participant was shown how to perform the Valsalva manoeuvre, which involves maintaining a seated position while holding your breath for 10 seconds at your maximum inspiration (Fig. 1B). For the purpose of identifying autonomic abnormalities (16, 17), the periflux blood flow decrease velocity (PDV) was developed (Fig. 1C). The studies were run at least three times soon before a dialysis session on two separate days, and the mean $\pm$ standard deviation were computed.

2.3. Heart Rate Variable

After determining PDV, patients were given 10 minutes to acclimatize on the treatment bed before having their surface electrocardiograms taken. From the acquired data, CVRR with the smallest SD were automatically extracted (18).

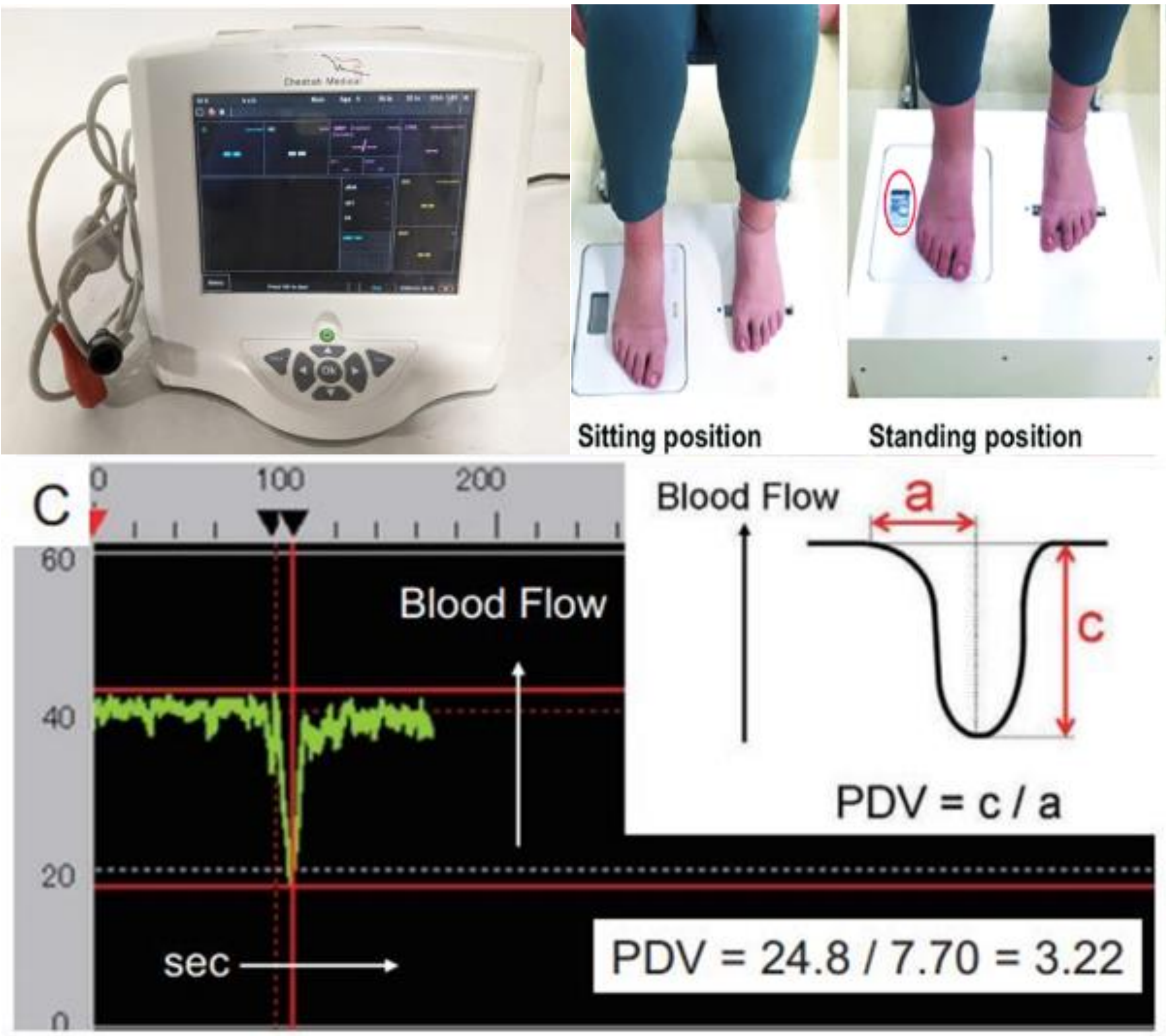

Figure 1 (A) Non-invasive continuous monitoring method (NICOMM) system is possible to measure skin tissue contained in a hemisphere with a diameter of 3 to 4 mm from the surface. (B) The participants maintained a seated position during the measurement. (C) Display shows periflux blood flow decreasing velocity (PDV) on the vertical axis and recorded time (sec) on the horizontal axis. The results are expressed in mL/min/100 g/.

2.4. Laboratory and Clinical studies

Prior to the first HD session of the week, blood samples were taken for haematological and biochemical analysis at the Kathmandu hospital laboratory after at least 12 hours of fasting. During HD, blood pressure (BP) was monitored hourly with a mercury sphygmomanometer. The means of measurements taken throughout 8 distinct weekly HD sessions, during which patients essentially demonstrated the same rise in body weight, were used to calculate the mean levels of systolic and diastolic blood pressure (22).

2.5. Sarpogrelate hydrochloride study

In this prospective and comparative investigation, the individuals who provided written informed consent for the experimental protocols were randomised and split into two groups. Sarpogrelate hydrochloride, a 5HT2A receptor blocker, was given orally to patients in group A (n=18; 12 men and 10 women; mean age, 60.1 ± 10.9 years old). The dose was 300 mg (100 mg three times daily). A placebo was administered as a control to the patients in group B (n=18; 7 men and 10 women; mean age, 65.2 ± 15.5 years old). Each medication was completely powdered and then put into identical capsules. PDV was assessed at 0, 2, and 4 months after the observation period began. Throughout the observation period, there was no medication change for any of the patients.

2.6. Statistical Analysis

Parametric and non-parametric data were compared using the two-sided t-test or the Mann-Whitney U analysis, respectively. Data were presented as mean values ± standard deviation. Using the Pearson correlation test, analyses were conducted to examine the association between PDV levels and various factors. Statistical significance was defined as a P-value < 0.05.

3. Results

Initially contrasted the PDV levels between healthy individuals and typical HD patients (Table 1). The typical PDV level was 3.79 ± 1.77 in HD populace contrasted to 8.72 ± 6.00 in controls, showing that uremic patients' autonomous activities were impaired in comparison to those of healthy controls even while they were receiving stable HD medication (Fig. 2, left panel). PDV levels combined across the HT and non-HT groups did not differ (Fig. 2, right panel). Following that, a straightforward linear regression analysis was carried out among the HD population to compare PDV levels to CVRR. According to Fig. 3, the PDV and CVRR had a strong positive connection (R=0.567, p0.001).

The outcome suggests that for measuring autonomic functions in HD patients, the PDV is just as helpful as a traditional parameter. Since numerous studies have demonstrated a high correlation between autonomic dysregulation and peripheral arterial stiffness (23), we assessed the connections between PDV levels and ABI and PWV. PDV and ABI have a strong positive connection (Fig. 4, left panel), however PWV and PDV do not (Fig. 4, right panel). but, PWV did not (Fig. 4, right panel). Low ABI scores indicate the presence of peripheral artery disease (25), while PWV analysis is a well-established diagnostic method for assessing general arteriosclerosis of major vessels (24).

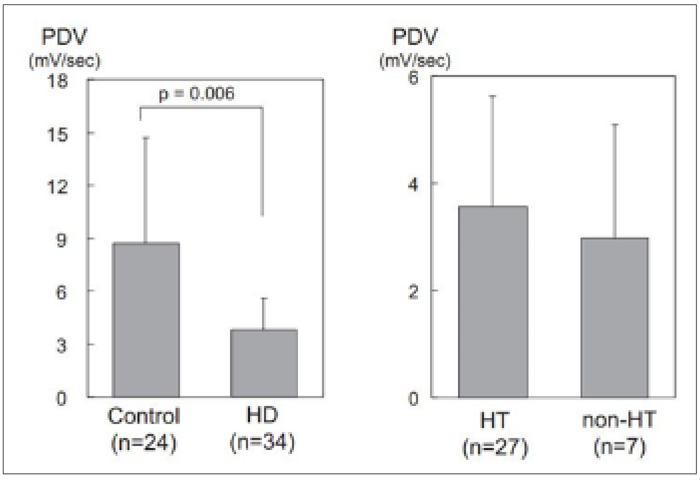

Figure 2 (left panel) Mean levels of PDV of 34 hemodialysis patients and 24 healthy controls. (right panel) Mean levels of PDV of 27 or 7 hemodialysis patients with or without hypertension, respectively. Data are mean ± SD.

Our findings indicate that in the HD population, parasympathetic dysfunction is primarily linked to peripheral vascular illness rather than big vessels. We investigated whether the PDV levels are altered when HD patients are categorized with or without oral administration of a 5-HT2A receptor blocker for three months, which is frequently used to treat PAD. Atherosclerosis is likely to contribute to the progression of autonomic dysfunction. There was no discernible difference between the two groups based on the laboratory and clinical data, which are presented in Table 2. When comparing the drug-administration group to the control group, we found no difference in the PDV levels (Fig. 5). The findings imply that short-term treatment with a 5HT2A receptor blocker, at least when given for a relatively brief amount of time like three months, does not improve autonomous function in individuals with typical HD.

Table 1 Characteristics of Participants in the Control and HD Groups

	Control	**HD**	
	(n=24)	(n=34)	p-value
Male : Female	13:11	12:12	
Age (years)	41.2 ± 15.8	61.1 ± 14.2	p < 0.002
Systolic BP	125 ± 16	132 ± 13	NS
Diastolic BP	71 ± 12	91 ± 11	NS
BMI (kg/m2)	34.5 ± 1.0	12.8 ± 3.4	p < 0.002
Laboratory data			
TP (g/dL)	7.0 ± 0.4	6.9 ± 0.4	NS
Alb (g/dL)	3.9 ± 0.3	3.8 ± 0.3	NS
UN (mg/dL)	19.8 ± 0.84	67.5 ± 10.3	p < 0.001
Cr (mg/dL)	0.9 ± 0.2	9.7 ± 2.9	p < 0.001
TG (mg/dL)	167.1 ± 80.3	151.0 ± 33.8	NS
HDLc (mg/dL)	35.0 ± 8.0	40.1 ± 10.6	NS

Data are means±SD, NS; nonsignificant. p < 0.05 is considered as significant. BP; blood pressure, BMI; body mass index, TP; total protein, Alb; albumin, UN; urea nitrogen, Cr; creatinine, TG; triglycerides, HDLc; high-density lipoprotein cholesterol.

4. Discussion

The most frequent reason for starting HD medication is DM nephropathy, and the average age of HD patients keeps rising yearly. As a result, there are more HD patients who experience autonomic dysfunction during or after HD sessions.

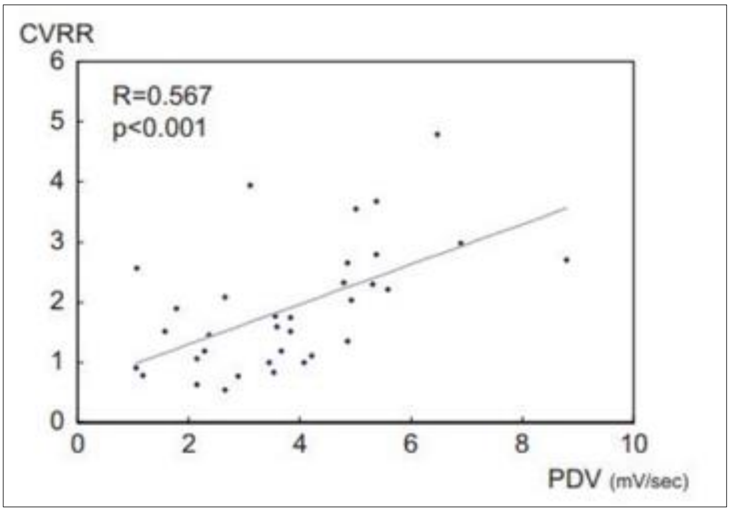

Figure 3 Correlation between PDV and coefficient of variation of R-R intervals (CVRR)

However, it is challenging to objectively and quantitatively evaluate the dysfunction, making it challenging to compare the severity of the dysfunction across numerous hospitals in diverse locations. The purpose of the study was to compare the new method with the traditional test in the HD population and assess the usefulness of a novel, noninvasive autonomic function measurement. Examining the impact of atherosclerosis on autonomous dysfunction in HD patients without DM or inadequate dialysis was another goal.

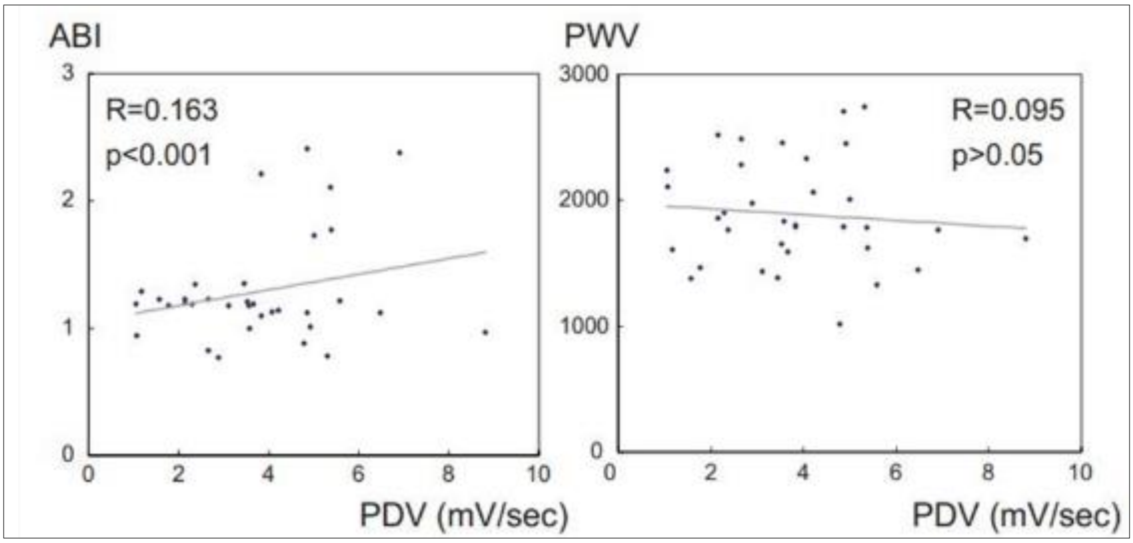

Figure 4 **(**A) Correlation between PDV and ankle-brachial blood pressure index (ABI). (B) Correlation between PDV and pulse-wave velocity (PWV)

Indicating that quantitative evaluation by LDF is comparable with clinical observation of cardiovascular autonomic impairment in various dialysis units, the mean level of PDV in HD patients is much lower than that in healthy controls. As far as we could tell, there is no information concerning the average PDV levels in the healthy and CKD population because the device used in the study is new. The huge variations in healthy control levels are most likely brought on by the very small number of participants or their extremely diverse backgrounds. The figure, however, is enough to show that there is a big gap between the two groups. We believe the tool is helpful for comparing time-course changes in autonomic dysfunction in each HD patient and among different dialysis centers in various areas. In CKD populations, heart rate responses to breathing have been used to assess parasympathetic nervous system activity (26). 60% of the subjects in Röckel etal's study on the alteration of heart rate and blood pressure responses to the Valsalva manoeuvre in chronic renal failure had aberrant heart rate responses to the manoeuvre (9). The novel gadget is not only trustworthy but also convenient for measurements at the bedside of a dialysis console, demonstrating that NICOMM is more appropriate for both clinical and experimental objectives than previous approaches.

In the CKD group, arterial stiffness has been shown to be a reliable predictor of all-cause death (27). In HD patients, baroreflex sensitivity is associated with peripheral arterial stiffness (23). As a measure of parasympathetic nerve activity, brachial-ankle PWV is inversely correlated with heart rate variability (28). According to Goernig et al., cardiovascular patients' heart rate variability is impacted by the severity of peripheral artery disease as determined by the ABI (29). Our findings demonstrate a substantial, positive connection between PDV and ABI, indicating that arterial vascular obstruction in HD patients has a greater impact on autonomic dysfunction than arterial stiffness. ABI and PWV both show changes in rather large vessels, therefore they don't reveal anything about small vessels.Our findings confirm a prior study by Goernig et al. Further research is needed on the intricate pathways behind autonomic neuropathy in uremic individuals. Sarpogrelate hydrochloride, a selective 5-HT2A antagonist, has been widely used to treat PAD because it is likely that atherosclerosis affects the progression of autonomic dysfunction as well as uremic toxins and diabetes in the HD population (30). This raises the question of whether the medication also improves parasympathetic dysfunction. Rats exhibit sympathoexcitation when their central 5-HT2A receptors are activated (31). Sarpogrelate hydrochloride reduces chronic pain brought on by diabetic neuropathy in people with type 2 diabetes, as demonstrated by Nishizawa et al. (32). Because of the observational duration, short-term use of the medication has no effect.

Even though patients with diabetes or those undergoing dialysis were excluded from the study, it is still possible that autonomous dysfunction in HD patients is brought on by complicated disorders such uremia, hypertension, etc. As underlying processes for diabetic neuropathy, disturbed microvascular circulation and elevated serotonin (5-HT) are thought to exist (33). It is desirable to administer the medication over time to assess how it affects autonomous dysfunction in people with kidney disease. More participants might be needed for long-term observation, nevertheless, in order to rule out the impact of other variables like medication other HD conditions.

The current studies show that measuring PDV by LDF is just as helpful for assessing autonomic function in HD patients as the standard approach.

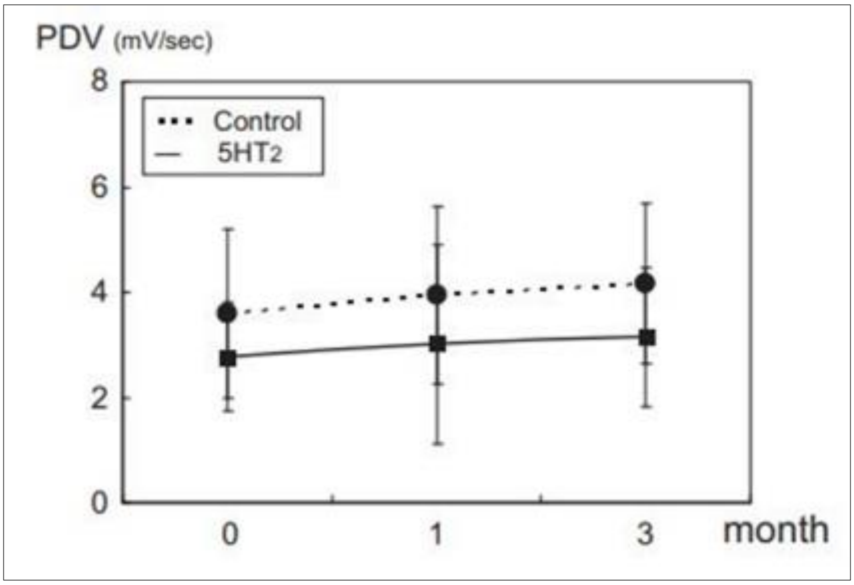

Figure 5 Effect of sarpogrelate hydrochloride on PDV in HD (n=17) patients compared with placebo (n=17).

Table 2 Characteristics of Participants with or without 5HT2A Receptor Blocker Administration

	Group A	**Group B**	
	(n=17)	**(n=17)**	**p-value**
Male : Female	11:10	7:12	
Age (years)	63.2 ± 14.8	63.1 ± 142.2	NS
Duration of Dialysis (month)	109.2 ± 109.0	98.7 ± 103.0	NS
Systolic BP (mmHg)	143 ± 14	131 ± 15	NS
Diastolic BP (mmHg)	66 ± 14	81 ± 12	NS
BMI (kg/m2)	32.7 ± 1.2	32.8 ± 5.4	NS
Dialysis efficiency (Kt/Vsp)	1.2 ± 0.3	1.3 ± 0.1	NS
Serum chemistry			
TP (g/dL)	3.0 ± 0.2	8.9 ± 0.2	NS
Alb (g/dL)	2.9 ± 0.1	2.8 ± 1.3	NS
UN (mg/dL)	20.8 ± 0.44	67.5 ± 10.3	NS
Cr (mg/dL)	1.9 ± 2.2	9.7 ± 2.9	NS
TG (mg/dL)	182.1 ± 82.3	151.0 ± 33.8	NS
HDL (mg/dL)	32.0 ± 8.1	50.1 ± 11.6	NS
E2MG (mg/dL)	37.6 ± 11.9	71.2 ± 9.5	NS

Data are means±SD BP; blood pressure, BMI; body mass index, TP; total protein, Alb; albumin, UN; urea nitrogen, Cr; creatinine, ủ2MG; ủ2-microglobulin, TG; triglycerides, HDL; high-density lipoprotein cholesterol, NS; nonsignificant. $p<0.05$ is considered as significant.

5. Conclusion

Additionally, in the HD population, there is a favourable correlation between PDV levels and ABI measurements of peripheral artery disease obstruction. The equipment is so easy to use that regular and straightforward PDV measurements provide us with useful data for treating HD patients more effectively. Regarding assessing autonomous functioning in hemodialysis patients, evaluation of PDV by LDF is just as effective as the standard approach. The benefit from regular and recurring assessments of autonomous dysfunction is made possible by the device's ease.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Statement of informed consent

The studies involving human participants were reviewed and approved by the Ethics Committee of the LSMU Ukraine. The patients/participants provided their written informed consent to participate in this study.

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