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Low central blood pressure and sympathetic activity predispose for the development of intradialytic hypotension

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Abstract

Intradialytic hypotension (IDH) may lead to a poor life quality and was associated with cardiovascular mortality in patients under hemodialysis. This study investigated the autonomic nerve and cardiovascular function in the IDH episodes.

In this case-control study, 70 end stage renal disease patients (198 visits) were recruited. Pulse wave analysis and heart rate variability were evaluated before hemodialysis. Two definitions of IDH were confirmed by medical records. IDH-f indicated a drop of systolic blood pressure or mean arterial pressure, accompanied with symptoms; IDH-n indicated a low nadir systolic pressure during the hemodialysis. All parameters were evaluated for the possible predisposing factors under each definition.

A total of 24 IDH-f and 37 IDH-n were noted in 177 visits. For both definitions, central pulse pressure seemed to be a consistent predisposing factor. Furthermore, lower sympathetic activity (odds ratio [OR] 0.55; 95% confidence interval [CI] 0.35–0.87), lower pulse pressure (OR 0.95; 95% CI 0.92–0.98), and higher augmentation index (OR 17.36; 95% CI 1.48–204.10) were the possible predisposing factors for IDH-f. On the contrary, lower mean arterial pressure (OR 0.87; 95% CI 0.78–0.98) was identified as the possible factor for IDH-n.

It was suggested that the lower central pulse pressure and sympathetic activity might be involved in the development of IDH.

Abbreviations: ACEi = angiotensin converting enzyme inhibitors, AI = augmentation index, ARB = angiotensin receptor blockers, CCB = calcium channel blockers, DBP = diastolic blood pressure, ESRD = end stage renal disease, GEE = generalized estimating equations, HD = hemodialysis, HF = high frequency, HR = heart rate, HRV = heart rate variability, IDH = intradialytic hypotension, LF = low frequency, MAP = mean arterial pressure, P = phosphorous, PP = pulse pressure, PWA = pulse wave analysis, RI = reflection index, SBP = systolic blood pressure, TP = total power, VLF = very low frequency.

Keywords: heart rate variability, intradialytic hypotension, pulse wave analysis

1. Introduction

Intradialytic hypotension (IDH), the hypotensive episode during hemodialysis (HD) procedure, was one of the major complications of HD. IDH did not only accompany with the discomfort but also implied the risk of cardiovascular disease.

The volume reduction was regarded as the main predisposing factor of IDH. However recent study have questioned this

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explanation, and the role of impaired compensatory mechanisms of cardiovascular system and plasma osmolality might be more important rather than volume reduction as a major cause.[1] Other studies also showed that IDH has complex pathophysiology, in which hemodynamic status and predialytic cardiovascular function evaluation were suggested.[2,3]

Pulse wave analysis (PWA) was widely used to evaluate the cardiovascular hemodynamics. Based on the wave reflection theory, augmentation index (AI) was defined as the ratio of augmentation pressure (reflection wave) over pulse pressure (PP) (reflection wave and forward wave) and it would be higher in a stiffer vessel. On the other hand, the activity of autonomic nervous function could be evaluated with heart rate variability (HRV), which has been associated with the outcomes of chronic renal disease.[4–6]

In stiffened arteries, steady perfusion might not be easily maintained because of the loss of buffering function which might be related to the hypotensive episodes during hemodialysis. In order to maintain a stable blood pressure, human body could activate various mechanisms, such as autonomic nervous system, renin-angiotensin-aldosterone system, and vasoactive hormones to fight against hypotension via the enhancement of cardiac output and total peripheral resistance. The failure of the above mechanisms under ultrafiltration, including impaired sympathetic activation, might lead to the decrease of total peripheral resistance, and together with inadequate plasma refill, the cardiac output would also decrease. Furthermore, diastolic dysfunction with poor ventricular filling as common problems in end stage renal disease (ESRD) patients might also decrease cardiac output due to less preload.[1,7]

It has been hypothesized that a ventricular underfilling and a low sympathetic activity with arteriolar vasodilation were related to IDH.[1] Previous studies have also demonstrated a low sympathetic activity during IDH.[8,9] However, the stiffened arteries and the sympathetic activity related to the development of IDH were not clearly understood. There seemed to be paradoxical interaction between sympathetic activity and vasoconstriction.

PWA and HRV together might provide more comprehensive information. The objective of this study was to evaluate the sympathetic activity and wave reflection before IDH episode, and to identify some possible predisposing factors for IDH.

There have been still some controversies about the definition of IDH. An adequate decrease of blood pressure, around 14 mm Hg change of systolic blood pressure (SBP) after HD, might lead to better prognosis than that of elevation and excessive decline of blood pressure.[10] Although IDH may accompany with impaired end-organ perfusion, there still an ambiguity existed regarding the difference between physical/pathological decrease of intradialytic blood pressure. Thus, this study applied 2 definitions of IDH as the outcome measures for the investigations of the underlying pathophysiological condition of IDH.

2. Material and methods

2.1. Study subjects

In this study, ESRD patients were invited to Chang Gung Memorial Hospital (Taoyuan, Taiwan). The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital (103–2699C). All methods were performed in accordance with relevant guidelines and regulations. Patients on regular HD (3 times per week) for at least 3 months were enrolled as the study subjects. The written informed consents were obtained from all the patients in the study. Subjects with arrhythmia, artery-vein anastomoses on both arms, or with other conditions which might interfere the evaluation of HRV and PWA were excluded.

With case-control study design, we have invited the patients by the order of bed number and asked for repeated measurements (3 times) in the following 1 month. IDH episode was noted in the medical record according to the 2 definition of IDH. One(IDH-f) was referred as Kidney Disease Outcomes Quality Initiative by National Kidney Foundation which was defined as a drop of systolic blood pressure ≥20 mm Hg or a drop of mean arterial pressure ≥10 mm Hg, accompanied with the presence of symptoms (fatigue, sighing, dizziness, restlessness, abdominal discomfort, nausea, or cramps, etc). While, the other (IDH-n) was defined as a nadir systolic pressure <90 mm Hg occurred during HD. Unstable general condition, such as fluctuated dry weight over 1 kg increase/decrease in the following 1 month, was also excluded.

2.2. Study design

All the HRV and PWA examinations were performed within 2 hours before regular dialysis in a lying position after 10 minutes of rest with normal breathing during the whole examination by the same operator in a quiet and air-conditioned room. Three electrodes were first settled on limbs and connected to a real-time HRV analyzer (KY-3, Yang-Ying Inc., Taiwan) to obtain 5 minutes electrocardiography.[11] The signals were stored and analyzed with a 10-bit analog-to-digital converter under a sampling rate of 512 Hz.

In order to obtain the radial pulse wave signals with auto-detected suitable pressure on the styloid process of non-artery-vein anastomoses wrist, a pressure-based system[12] with a sampling rate of 500 Hz was then applied. Having been known as pulse volume plethysmography, this could be used to evaluate the intra-arterial pulse wave contour by a cuff sphygmomanometer.[13] The pulse wave was calibrated by SBP and diastolic blood pressure (DBP) on the non-artery-vein anastomoses side recorded by ANSWatch wrist sphygmomanometer (Taiwan Scientific Corporation, Taipei, Taiwan. Taiwan Food and Drug Administration certificate number: 001525) with a biosensor array embedded in the wearing cuff and was analyzed automatically for the hemodynamic parameter by custom-designed program (v1.02, Chen-Huan Chen, MD) on a commercial software package (Matlab, version 4.2, The MathWorks, Inc.).

Intradialytic blood pressure was obtained by dialysis machine with ambulatory blood pressure monitoring (brachial artery level) at every 1 hour and the timing of possible IDH or intradialytic hypertension. Follow up twice within 1 month would be evaluated for the paired samples of episodes/non-episodes.

2.3. Data analysis

2.3.1. HRV analysis. The R-R intervals were transformed to power spectrum through frequency-domain analysis with nonparametric method of Fourier transformation. Three standard frequency-domain measurements were quantified as very low frequency (VLF), low frequency (LF), and high frequency (HF).[4] The variance of R-R intervals, equal to the sum of LF, HF, and VLF would be the total power (TP) in the frequency domain. Since LF represented both vagal and sympathetic

activities, and HF represented the vagal activity, the normalization of LF (LF% = LF/(total power-VLF) × 100) could be applied to evaluate the sympathetic activity. The ratio of low frequency power over high frequency power (LF/HF) would also reflect sympathovagal balance or the sympathetic modulations. According to previous study, in order to eliminate the possible skewed distribution, all the parameters, except LF% and HF%, were transformed into natural logarithmic form.[11]

2.3.2. Central PWA. In this study, radial pulse wave was transformed to central pulse wave based on generalized transfer function.[14] The 10-second pulse waves were ensemble-averaged into a single wave. Furthermore, triangulation method, a method matching a triangular-shaped wave as the pseudo-flow waveform on the timing of foot, inflection point, and incisura of the central pulse wave, would be used to reconstruct the forward and reflected wave.[15] This valid method was already applied in epidemiological study and showed good results for long term cardiovascular mortality.[15] The central pulse wave and forward wave/reflection wave would be analyzed separately. For central wave analysis, central SBP, DBP, PP, and central AI would be analyzed. AI, the ratio of PP on late systolic peak and early systolic peak defined by the derivative method, reflected the severity of arterial stiffness.[16,17] Compliance was estimated by the decay constant of the diastolic part of the pulse wave with natural log transformed, and was validated with invasive examination.[18]

For reflection wave analysis, the central pulse wave would be decomposed into its forward wave and backward wave with Pf(t) and Pb(t) as the amplitudes respectively, by using triangulation method and the following equations.

$$pf(t) = [Pm(t) + Zc \times F(t)]/2$$

$$pb(t) = [Pm(t) + Zc \times F(t)]/2$$

where Zc is characteristic impedance, Pm(t) is the original central wave, and F(t) is the approximated triangular-shaped flow wave.

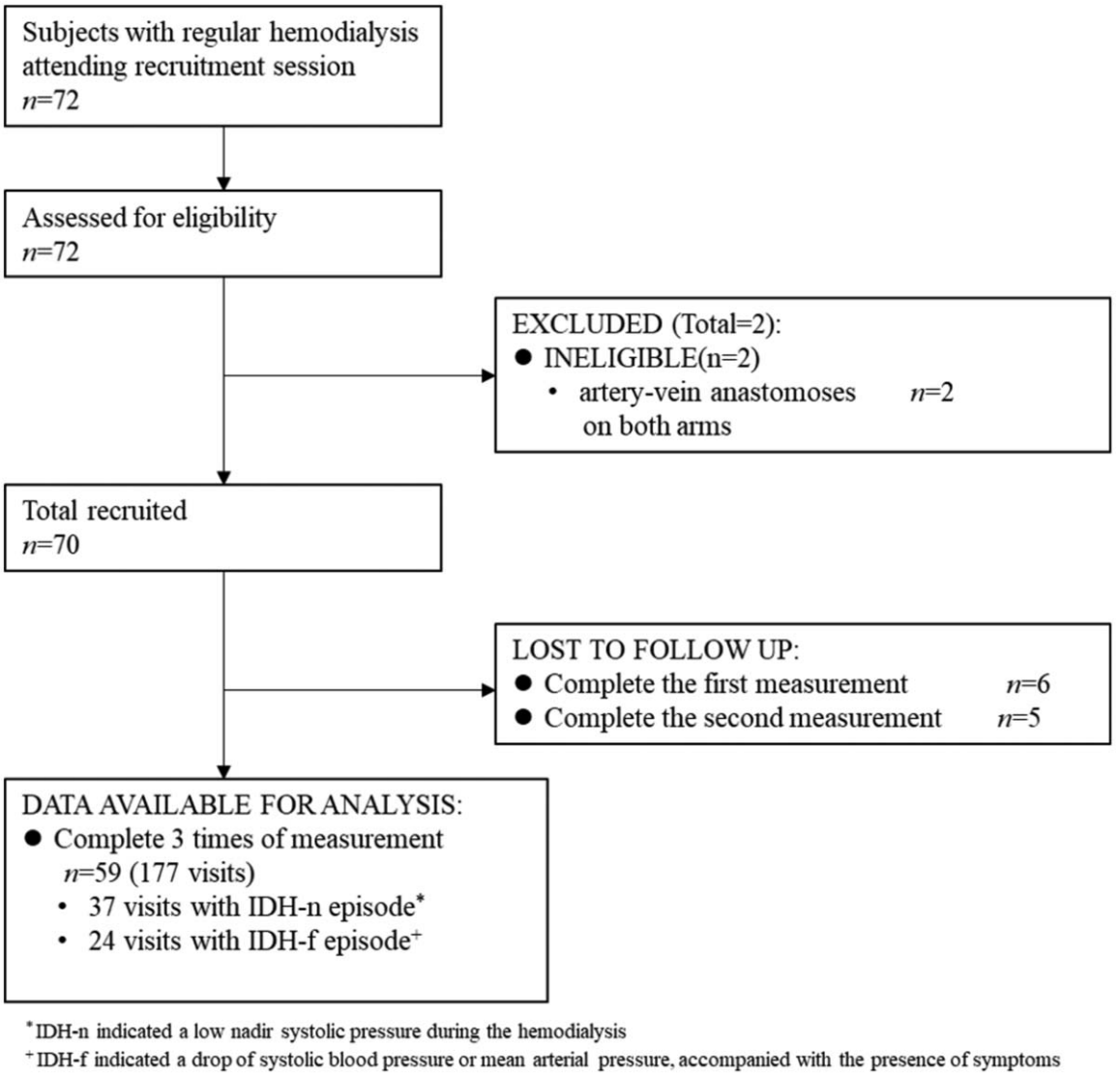

Figure 1. Flow chart of patients' enrollment.

Table 1

Baseline demographic characteristics and dialysis data of all subjects.

	Range	Mean ± SD
Age (years)	34–84	60.5 ± 12.0
Height (cm)	147–177	159.2 ± 8.0
Dry weight (kg)	33.5–86.0	55.9 ± 10.8
Body mass index (kg/m^2)	14.9–28.5	22.0 ± 3.1
Predialytic body weight (kg)	35.5–89.6	58.4 ± 11.4
Interdialytic weight gain (kg)*	−0.6–5.4	2.5 ± 1.1
Postdialytic body weight (kg)	33.7–85.8	55.9 ± 10.7
Ultrafiltration amount (kg)	0.4–5.4	2.5 ± 1.1
Initial dialysate temperature (°C)	35–37	36.4 ± 0.6
Initial blood flow rate (ml/min)	200–350	286.6 ± 36.7
Dialysis vintage (months)	7–416	130.4 ± 101.5
Hematocrit (%)	25.2–43.3	33.0 ± 3.7
P (mg/dl)	8.1–11.2	9.6 ± 0.8
Ca (mg/dl)	1.7–8.0	4.7 ± 1.4
Predialytic SBP (mm Hg)	76–212	143.9 ± 29.9
Predialytic DBP (mm Hg)	44–102	72.6 ± 13.5
Predialytic PP (mm Hg)	13–153	71.3 ± 26.6
Predialytic MAP (mm Hg)	63–125	96.4 ± 16.2
Predialytic HR (beats/min)	56–100	78.7 ± 11.5
	N	
Gender (F)	28 (47%)	
Gender (M)	31 (53%)	
Hypertension	15 (25%)	
Diabetes mellitus	16 (27%)	
Stroke	3 (5%)	
Medication history (within one month)		
ACEi	6 (10%)	
ARB	2 (3%)	
beta blockers	8 (14%)	
CCB	9 (15%)	
Diuretics	3 (5%)	
Vasodilator	1 (2%)	
Midodrine	3 (5%)	

ACEi = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blockers, CCB = calcium channel blockers, DBP = diastolic blood pressure, HR = heart rate, MAP = mean arterial pressure, PP = pulse pressure, SBP = systolic blood pressure.

* The interdialytic weight gain is defined as the difference between the pre-dialytic body weight and dry weight.

Furthermore, the amplitudes of forward and backward wave could be used to calculate the reflection index (RI, = [Pb/(Pf +Pb)]).[15]

2.4. Statistical analysis

Baseline characteristics were presented as mean ± SD (standard deviation) or counts (percentages), appropriately.

Possible predisposing factors were assessed by using the generalized linear models with generalized estimating equations (GEE). A GEE assuming a logit link function and an exchangeable correlation was used to estimate the correlation raising from 1 subject followed up twice or above. After estimation, P value $< .20$ was considered as candidate for adjustment of confounders. However, if the P value was considered, the ultrafiltration amount might be artificially changed due to the IDH episodes, and the ultrafiltration amount was excluded, leaving interdialytic weight gain in the following analysis.

In order to analyze the association between all interesting variables and outcomes, the generalized linear models with generalized estimating equations were used, assuming a logit link function, an exchangeable correlation, and adjustment for all confounders in the model.

All statistical assessments were evaluated at a two-sided significance level of 0.05. Analyses were performed with SAS software package, version 9.2 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline demographic characteristics and dialysis data

In this study, we recruited 70 patients (198 visits) under regular HD. After excluding the patients without completion of 3 visits in 1 month, 59 patients (177 visits including 37 IDH-n episodes and 24 IDH-f episodes) were included in the following analysis. All the 59 patients had stable dry weight (within 1 kg fluctuation) during the study (Fig. 1). Demographic data of the first visit of each patient is shown in Table 1. The mean ultrafiltration amount was found to be 2.5 ± 1.1 kg and the initial blood flow rate was

Table 2

HRV and PWA parameters in IDH-n/IDH-f episode.

	IDH-n Mean ± SD	IDH-f Mean ± SD	Both episodes Mean ± SD	No episode Mean ± SD
ln (TP)	5.66 ± 1.66	4.97 ± 1.53	4.86 ± 1.29	5.72 ± 1.47
ln (VLF)	4.79 ± 1.87	3.46 ± 2.08	3.83 ± 1.72	4.73 ± 1.64
ln (LF)	3.82 ± 2.09	3.07 ± 1.82	2.69 ± 1.88	3.85 ± 1.62
ln (HF)	3.60 ± 1.69	2.99 ± 1.80	3.01 ± 1.38	3.49 ± 1.88
LF%	0.20 ± 0.13	0.22 ± 0.19	0.17 ± 0.15	0.18 ± 0.11
ln (LF/HF)	0.22 ± 1.06	0.08 ± 1.21	−0.32 ± 1.01	0.38 ± 1.13
HF%	6.93 ± 4.74	5.28 ± 5.54	6.44 ± 6.21	7.45 ± 6.29
Central SBP (mm Hg)	109.7 ± 22.6	117.5 ± 24.4	114.9 ± 26.9	126.9 ± 23.2
Central DBP (mm Hg)	63.5 ± 8.7	65.5 ± 9.6	64.1 ± 8.9	63.8 ± 10.1
Central MAP (mm Hg)	67.6 ± 8.2	68.7 ± 8.6	68.2 ± 8.3	72.8 ± 10.2
Central PP (mm Hg)	81.6 ± 12.0	85.0 ± 10.8	83.7 ± 13.2	90.8 ± 12.9
Compliance (ml/mm Hg)	1.08 ± 0.90	0.97 ± 0.94	1.04 ± 1.07	0.99 ± 0.67
Central AI	0.51 ± 0.13	0.50 ± 0.12	0.51 ± 0.11	0.47 ± 0.13
RI	0.41 ± 0.03	0.40 ± 0.04	0.41 ± 0.03	0.40 ± 0.04
Pb (mm Hg)	12.5 ± 5.9	14.7 ± 7.0	14.9 ± 7.6	16.4 ± 5.4
Pf (mm Hg)	17.8 ± 8.9	22.1 ± 11.0	21.6 ± 11.2	24.8 ± 8.6

177 visits included 37 IDH-n episodes and 24 IDH-f episodes. There were 15 visits with both IDH-n and IDH-f episodes, and 131 visits without IDH episode.

Table 3

Univariate analysis for the baseline data in IDH-f.

	Univariate analysis			
	OR	95% CI		*P* value
Age (years)	0.99	0.95	1.03	.651
Gender (F)	1.04	0.27	4.05	.955
Gender (M)	1.00	1.00	1.00	.
Height (cm)	1.04	0.98	1.10	.234
Dry weight (kg)	1.02	0.97	1.07	.440
Body mass index (kg/m^2)	1.00	0.82	1.22	.994
Predialytic body weight (kg)	1.02	0.96	1.07	.587
Interdialytic weight gain (kg)	1.74	1.14	2.65	.010*
Ultrafiltration amount (kg)	1.48	0.94	2.33	.093
Initial dialysate temperature (°C)	0.77	0.39	1.52	.448
Initial blood flow rate (ml/min)	1.00	0.99	1.01	.845
Dialysis vintage (months)	1.00	1.00	1.00	.898
Hematocrit (%)	1.12	0.99	1.27	.083
P (mg/dL)	1.45	1.04	2.02	.027*
Ca (mg/dL)	0.80	0.46	1.36	.406
Predialytic SBP (mm Hg)	1.01	0.99	1.03	.176
Predialytic DBP (mm Hg)	1.04	1.00	1.07	.026*
Predialytic PP (mm Hg)	1.01	0.99	1.03	.539
Predialytic HR (beats/min)	1.02	0.98	1.06	.314

IDH = intradialytic hypotension.
* $P \leq .05$.

found to be 286.6 ± 36.7 (ml/minute). Nineteen subjects had antihypertensive medication and 3 subjects have midodrine in recent 1 month (6 angiotensin converting enzyme inhibitors, 2 angiotensin receptor blockers, 8 beta blockers, 9 calcium channel blockers, 3 diuretics, and 1 vasodilator). There was no significant difference between groups in medication history. The antihypertensive drugs were taken in non-HD day, and no midodrine was used in the visit day of this study. (Table 1)

Besides, HRV and PWA parameters in whether IDH-n or IDH-f episode were shown in Table 2.

3.2. IDH-f

In the analysis for IDH-f, the baseline univariate analysis showing the interdialytic weight gain, phosphorous(P) and predialytic DBP was significantly associated with the episodes of IDH-f (odds ratio [OR]:1.74, 1.45, 1.04, respectively). Factors with *P* value <.20, including hematocrit, P, predialytic SBP, predialytic DBP, interdialytic weight gain, were selected as confounders for the adjustment in the analysis for HRV and PWA (Table 3).

Among HRV and PWA parameters, ln(TP), ln(VLF), ln(LF), central DBP, and central PP were significant determinants (odds ratio [OR]: 0.68, 0.68, 0.71, 1.03, and 0.97, respectively) in univariate analysis. The multivariate analysis showed that the increase in ln(VLF), ln(LF), ln(LF/HF), central PP and central AI values was associated with lower ratio of occurring vs not occurring IDH-f (OR per 1 unit = 0.69, 95% CI:0.54–0.90, *P* = .005, OR per 1 unit = 0.70, 95% CI:0.49–0.99, *P* = .046, OR per 1 unit = 0.55, 95% CI:0.35–0.87, *P* = .011, OR per 1 unit = 0.95, 95% CI:0.92–0.98, *P* = .004, respectively). The increase in central AI values was associated with higher ratio of occurring vs not occurring IDH-f (OR per 1 unit = 17.36, 95% CI:1.48–204.10, *P* = .023) (Table 4).

3.3. IDH-n

In the analysis of IDH-n, the baseline univariate analysis showed that dialysis vintage, predialytic SBP and predialytic PP were significantly associated with the episodes of IDH-n (odds ratio [OR]: 1.01, 0.98, 0.98, respectively). Factors with *P* value <.20, including predialytic SBP, Initial dialysate temperature, dialysis vintage and Interdialytic weight gain was selected as confounders for adjustment in the analysis for HRV and PWA (Table 5).

Among HRV and PWA parameters, only central PP (mm Hg) was found to be a significant determinant (odds ratio [OR]: 0.98) in univariate analysis. Multivariate analysis showed that 1 unit increased in central mean arterial pressure (MAP) was associated with 0.87 (95% CI: 0.78–0.98, *P* = .026) times the ratio of occurring vs nonoccurring of IDH-n (Table 6).

Table 4

Univariate and Multivariate analysis for HRV and PWA parameters in IDH-f.

	Univariate analysis				Multivariate analysis			
	OR	95% CI		*P* value	OR	95% CI		*P* value
ln (TP)	0.68	0.48	0.95	.026*	0.70	0.47	1.05	.087
ln (VLF)	0.68	0.54	0.85	.001*	0.69	0.54	0.90	.005*
ln (LF)	0.71	0.54	0.94	.017*	0.70	0.49	0.99	.046*
ln (HF)	0.82	0.62	1.08	.162	0.92	0.71	1.20	.531
LF%	4.88	0.12	202.61	.404	1.40	0.04	44.42	.849
ln (LF/HF)	0.79	0.54	1.17	.240	0.55	0.35	0.87	.011*
HF%	0.92	0.80	1.05	.223	0.94	0.83	1.06	.296
Central SBP (mm Hg)	1.00	0.97	1.02	.692	0.99	0.96	1.01	.330
Central DBP (mm Hg)	1.03	1.00	1.05	.030*	1.01	0.98	1.03	.623
Central MAP (mm Hg)	0.99	0.95	1.03	.659	0.99	0.96	1.02	.356
Central PP (mm Hg)	0.97	0.94	0.99	.022*	0.95	0.92	0.98	.004*
Compliance (ml/mm Hg)	1.00	0.97	1.03	.939	0.86	0.65	1.15	.315
Central AI	4.91	0.33	72.94	.248	17.36	1.48	204.10	.023*
RI	0.25	0.00	5751.41	.789	284.20	0.01	6101805	.267
Pb (mm Hg)	0.98	0.87	1.10	.690	0.95	0.81	1.11	.497
Pf (mm Hg)	0.99	0.92	1.05	.683	0.95	0.86	1.04	.233

AI = augmentation index, HF = high frequency, HRV = heart rate variability, LF = low frequency, PWA = pulse wave analysis, RI = reflection index, TP = total power, VLF = very low frequency.
Confounder in multivariate analysis: hematocrit, P, predialytic SBP, predialytic DBP, Interdialytic weight gain.
* $P \leq .05$.

Table 5

Univariate analysis for the baseline data in IDH-n.

	Univariate analysis			
	OR	95% CI		*P* value
Age (years)	0.98	0.95	1.01	.263
Gender (F)	1.39	0.40	4.78	.602
Gender (M)	1.00	1.00	1.00	.
Height (cm)	0.96	0.88	1.04	.311
Dry weight (kg)	0.98	0.93	1.03	.503
Predialytic body weight (kg)	0.97	0.92	1.03	.341
Interdialytic weight gain (kg)	1.41	0.96	2.07	.076
Body mass index (kg/m^2)	0.95	0.80	1.11	.498
Ultrafiltration amount (kg)	1.26	0.84	1.90	.266
Initial dialysate temperature (°C)	1.49	0.85	2.60	.161
Dialysis vintage (months)	1.01	1.00	1.01	<.001*
Initial blood flow rate (ml/min)	1.00	0.99	1.01	.919
Hematocrit (%)	1.07	0.96	1.19	.237
P (mg/dl)	0.83	0.59	1.17	.296
Ca (mg/dl)	1.19	0.65	2.18	.568
Predialytic SBP (mm Hg)	0.98	0.96	1.00	.019*
Predialytic DBP (mm Hg)	0.99	0.97	1.02	.532
Predialytic PP (mm Hg)	0.98	0.96	0.99	.008*
Predialytic HR (beats/min)	1.00	0.97	1.03	.751

* $P \leq 0.05$.

4. Discussion

Low central blood pressure was noted before the IDH episode. Together with the paradoxical interaction between decreased sympathetic activity and vasoconstriction, the role of cardiovascular function in predialytic evaluation has been revealed in this study.

According to our knowledge, this was the first study to investigate the predictive values of predialytic hemodynamic conditions for 2 forms of IDH. In this study, 2 definitions of IDH have shown different characteristics in the baseline demographic data, HRV and PWA parameters, suggesting the different pathophysiologies of them.

In this study, we noted that the episodes of IDH-f were related to volume reduction with greater interdialytic weight gain. The arterial stiffness with higher phosphorus (P) level and central AI might also be the predisposing factors of IDH-f. The lower ln(LF) and ln(LF/HF) and lower central PP might reflect the role of lower sympathetic activity and lower stroke volume in IDH-f. In the other hand, a longer dialysis vintage with possible vascular ageing and a lower predialytic blood pressure in SBP, PP, MAP, and central PP in IDH-n showed different characteristics.

In this study, patients with IDH-n had a longer dialysis vintage associated with a lower predialytic SBP ($r = -0.441$, $P < .001$, for the first visit of the 59 patients in our data). Besides, another study of pulse wave velocity indicated that the arterial stiffness progressed with ageing and longer dialysis vintage.[19] However, in this study, in contrary to the dialysis vintage, age itself did not play an important role either in IDH-f or IDH-n.

Volume reduction was known as a factor for the IDH-f. The greater interdialytic weight gain following the greater intradialytic volume reduction might raise the risk of IDH-f. Another study demonstrated that higher stroke volume variation might be an independent predictor of IDH (defined as a drop of MAP $\geq$10 mm Hg), which was in good agreement with the present study.[20] However, only weak association was noted between interdialytic weight gain and IDH-n in our experimental data. This implied that the volume fluctuation was the important challenge of IDH-f, whereas the episode of IDH-n might be resulted from chronic pathophysiological condition with longer dialysis vintage.

The pathophysiological role of predialytic blood pressure remained to be elucidated. Not only low but also high predialytic blood pressure might be the predisposing factor of IDH.[21–23] In this study, the experimental data suggested that higher phosphorus and higher predialytic DBP were associated with IDH-f. Ana Rocha et al also observed the similar finding in patients with older age, which correlated with vascular calcification and arterial stiffness.[24]

In fact, higher predialytic peripheral blood pressure might mislead the evaluation. Because the difference between predialytic and intradialytic SBP was included in the definition of IDH-f,

Table 6

Univariate and multivariate analysis for HRV and PWA parameters in IDH-n.

	Univariate analysis				Multivariate analysis			
	OR	95% CI		*P* value	OR	95% CI		*P* value
ln (TP)	1.04	0.87	1.25	.663	0.92	0.74	1.14	.420
ln (VLF)	1.06	0.93	1.21	.397	0.94	0.83	1.07	.378
ln (LF)	1.03	0.85	1.24	.750	0.90	0.70	1.16	.420
ln (HF)	1.07	0.96	1.21	.226	1.02	0.87	1.20	.803
LF%	0.95	0.10	9.11	.964	1.09	0.12	10.10	.942
ln (LF/HF)	0.86	0.62	1.20	.384	0.74	0.50	1.10	.134
HF%	0.99	0.95	1.03	.720	0.96	0.89	1.04	.339
Central SBP (mm Hg)	0.98	0.97	1.00	.104	0.94	0.84	1.05	.264
Central DBP (mm Hg)	0.97	0.93	1.02	.189	1.01	0.93	1.09	.892
Central MAP (mm Hg)	0.97	0.94	1.00	.075	0.87	0.78	0.98	.026*
Central PP (mm Hg)	0.98	0.96	0.99	.004*	0.89	0.78	1.01	.082
Compliance (ml/mm Hg)	1.18	0.76	1.81	.461	0.38	0.14	1.08	.071
Central AI	1.60	0.24	10.70	.631	18.20	0.09	3534.54	.280
RI	35.42	0.08	16629	.256	137.44	0.05	377100	.223
Pb (mm Hg)	0.96	0.87	1.06	.438	0.88	0.54	1.45	.618
Pf (mm Hg)	0.95	0.89	1.00	.069	0.92	0.70	1.22	.572

Confounder in multivariate analysis: predialytic SBP, Initial dialysate temperature, Dialysis vintage, Interdialytic weight gain.
* $P \leq .05$.

a drop of SBP may be noted more easily in session with high predialytic SBP. On the other hand, under the definition of IDH-n, lower but not higher predialytic blood pressure might be associated with IDH episodes.

After the adjustment of the confounders including the predialytic SBP, we noted that lower central PP was associated with IDH-f and that lower central PP and lower MAP were associated with IDH-n. These indicated that lower cardiac output might be the common manifestation in 2 definitions. This was mainly because of the reason that the stroke volume from left ventricle and aortic properties (characteristic impedance) determined the level of central PP. Despite the lack of statistical significance, lower forward wave (Pf) and lower reflection wave (Pb) were noted both in IDH-f and IDH-n, indicating the lower stroke volume.

One of the most interesting finding of this study was that the higher central AI was noted before the IDH-f episode, implying that the arterial stiffness might be an important factor, which was independent of interdialytic weight gain and predialytic blood pressure.

Some research showed the correlation between vascular calcification and IDH under compound definition (nadir SBP <90 mm Hg or request for the administration of bolus fluid occurring over 2 times in 10 HD session).[25,26] Other study also showed that hyperphosphatemia might induce vascular calcification and increase the cardiovascular mortality in ESRD patients.[27–29]

For IDH-n definition, we showed the higher central AI ($P=.043$) in patients with repeated IDH-n episodes from our previous study.[30] However, in current study, we focused on every single episode and noted that the correlation with wave reflection, which was also indicating that the arterial stiffness, was less prominent in the multivariate analysis with blood pressure.

In this study, lower LF and LF/HF noted before IDH-f, representing the lack of vascular tone, might be confused with the high central AI and phosphorus level, which might reflect the arterial stiffness. In the previous study, Chen et al reported the vasoconstrictors (endothelin-1 and angiotensin II) in patient with IDH-f experience (at least 3 times in 1 month) was higher before HD and lower after HD, reflecting a poorer vasoconstrictive response for volume reduction.[31] Other study also observed the lower sympathetic activity[5] and poorer sympathetic response[8] in IDH patients. Thus, according to our data, it was expected that both arterial stiffness and sympathetic malfunction might contribute to the episodes of IDH-f.

Some researchers presumed that the Bezold-Jarisch reflex, a protective mechanism to prevent the excessive left ventricular pressure by sympatho-inhibitory cardiodepressor activation and peripheral vasodilatation, contributed to IDH.[32] Beside of chemosensitive receptors, mechano-receptor stimulated by the elevation of left ventricular pressure was also found for eliciting Bezold-Jarisch reflex.[33]

In fact, arteriolar vasoconstriction and arterial stiffness might enhance the augmentation of reflection wave on the central pressure (higher AI) leading to higher left ventricular afterload and lower coronary perfusion, representing a possible negative impact on the cardiovascular system.[34] Thus, high AI and Bezold-Jarisch reflex might be a clue for us to investigate IDH-f.

In the other way, the pathophysiology of VLF was still unknown, but some evidence showed the correlation between low VLF and poor cardiac defensive response to compensate an external stress.[35] In part, it might explain the poor compensatory mechanisms of IDH-f in this study.

In this study, we have observed that a low central PP together with low sympathetic tone and arterial stiffness in predialytic stage, might contribute to a fragile condition and a drop of blood pressure under ultrafiltration. Thus, IDH-f might reflect an unstable cardiovascular condition, which resulted into a fluctuation of blood pressure and intradialytic morbidities.

On the other hand, patients with long dialysis vintage might maintain relatively a low blood pressure either in predialytic or interdialytic stage. Compared to the blood pressure fluctuation of IDH-f, IDH-n might reflect a chronic hypotensive condition.

In this study, PWA revealed some predisposing factors for IDH in blood pressure, arterial stiffness, and the forward/reflected wave. However, the information of cardiac output may be limited with this technique. Other information, such as Doppler echocardiography, may be applied in further confirmation and the future study.

5. Conclusion

In this study, we have found some possible predisposing factors for IDH with HRV and PWA. Central PP, determined by both characteristic impedance and forward flow, seemed to be a consistent marker in the prediction of 2 IDH definitions. However, 2 IDH definitions might have distinct cardiovascular hemodynamics. Lower sympathetic activity, lower PP and higher AI were the possible predisposing factors for the episodes of IDH-f. On the contrary, lower MAP was found to be the possible predisposing factor for the episodes of IDH-n. Thus, in order to investigate the cardiovascular condition before HD session, the informative factors more than the blood pressure would be necessarily important.

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