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Relationship between blood pressure response during hemodialysis and exercise tolerance or heart rate recovery measured using cardio-pulmonary exercise testing in maintenance hemodialysis patients

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Abstract

Background: This study investigated the association between the blood pressure response during hemodialysis (HD) and exercise tolerance or heart rate recovery (HRR) measured with cardiopulmonary exercise testing (CPX).

Methods: The study enrolled 23 patients who had been undergoing 4-h regular maintenance HD. The maximum workload ($Load_{peak}$), peak oxygen uptake (VO_{2peak}), workload and oxygen uptake at the anaerobic threshold ($Load_{AT}$ and VO_{2AT} , respectively), and HRR were measured with CPX. The average systolic blood pressure during HD (SBP_{av}) was measured, and the number of times the SBP was less than 100 mmHg was determined in the 2-week period after CPX.

Results: The SBP_{av} showed a significant correlation with $Load_{AT}$ ($r = 0.46$) and $Load_{peak}$ ($r = 0.43$, $p < 0.05$). The number of times the SBP was less than 100 mmHg showed a significant correlation with the HRR ($r = -0.44$, $p < 0.05$).

Conclusion: Exercise intolerance and HRR in HD patients may be associated with blood pressure instability during HD.

Keywords: Blood pressure instability, Cardio-pulmonary exercise testing, Exercise tolerance, Heart rate recovery, Hemodialysis

Introduction

The most frequent and serious side effect of hemodialysis (HD) is intradialytic hypotension (IDH) [1], which is estimated to occur in 15% to 30% of all HD treatments [2, 3] and is an independent risk factor for mortality [4]. The main causes of IDH have been reported to include acute hypovolemia during ultrafiltration and inadequate compensatory mechanisms [5] associated with inadequate dry weight setting, hypoalbuminemia that induces the reduction of the plasma

refilling rate, reduced cardiac function, and abnormalities in the autonomic nervous system [6]. Assuming that the dry weight and albumin levels are managed appropriately, it is hypothesized that blood pressure changes can occur with ultrafiltration when the cardiovascular and autonomic responses cannot compensate for large volume losses.

Blood pressure responses are associated with exercise tolerance [7]. The peak oxygen uptake (VO_2), which is one of the exercise tolerance parameters measured by cardio-pulmonary exercise testing (CPX), may affect the blood perfusion to the peripheral tissues because it indicates not only the ability for oxygen utilization (arterial-venous O_2 difference) but also oxygen supply (cardiac output). Previous studies have shown that the exercise

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tolerance rate in HD patients is ~50–60% of that in normal subjects [8, 9] and that left ventricular (LV) function in HD patients is also decreased [10, 11]. Moreover, HD patients have an autonomic dysfunction [12], which is even more common in patients with uremia and IDH [12, 13]. These data suggest that the exercise intolerance in HD patients leads to instability of blood pressure through poor blood perfusion in the peripheral tissues resulting from a decreased vascular function due to autonomic dysfunction. However, to our knowledge, only a few studies have investigated the relationship between exercise tolerance and IDH. To elucidate the factors affecting the pathological response of IDH, firstly, it is necessary to clarify the relationship between exercise and the near-normal blood pressure response by ultrafiltration.

The purpose of this study is to assess the relationship between exercise tolerance and blood pressure response during HD. Moreover, the heart rate recovery (HRR) was measured using CPX and calculated from the absolute difference between the peak heart rate (HR) and HR in 1 min of recovery, which reflects the autonomic function. Exercise tolerance and the HRR may reflect the blood pressure response during HD.

Materials and methods

Patients

Twenty-three patients with chronic kidney disease who had been undergoing 4-h regular maintenance HDs, three times per week for >2 years, were enrolled. The following patients were excluded from this study: patients with serious hypotension at least 1 month prior to this study, including symptomatic hypotension and/or requiring cessation of fluid removal or treatment with medication, and patients who have contraindications for exercise testing according to cardiovascular disease established guidelines for rehabilitation [14] (e.g., acute myocardial infarction, uncontrolled unstable angina pectoris, and uncontrolled arrhythmia), severe morbid obesity (body mass index (BMI) of >30 kg/m²), moderate or severe heart valve insufficiency and/or stenosis, history of stroke, chronic obstructive pulmonary disease, and orthopedic or musculoskeletal disorder. Patients taking beta blockers were also excluded to exclude the influence on the HR during exercise. This study conformed to the provisions of the Declaration of Helsinki, and written informed consent was obtained from all participants. The study was approved by the Nagoya Kyoritsu Hospital Ethical Committee (K118-02).

Exercise testing

Symptom-limited CPX was performed using a cycle ergometer (STB-1400, NIHON KOHDEN, Tokyo, Japan) according to a ramp protocol. After resting for 3 min on

the cycle ergometer, exercise was started with an increment of load of 10 watt/min following a 3-min warm-up period. Twelve-lead ECG findings were continuously monitored. The HR and systolic and diastolic blood pressures (SBP and DBP) were monitored every 1 min during the testing. VO₂, carbon dioxide production, and tidal volume were measured using a breath-by-breath method and an expired gas analyzer (AE310s, MINATO, Tokyo, Japan) during CPX. The endpoint of CPX was determined in accordance with the criteria of the American College of Sports Medicine. CPX performed the evaluation on inter-dialytic days. None of the patients showed ischemic ECG changes during CPX.

The maximal symptom-limited workload (Load_{peak}) was defined as the highest work level reached. Peak VO₂ (VO_{2peak}) was considered as the highest VO₂ obtained. The anaerobic threshold was defined using the *v*-slope method, and VO₂ (VO_{2AT}) and workload at (Load_{AT}) were measured. The HR at rest, AT, and peak exercise (HR_{peak}) were determined from the HR recorded during CPX. In addition, the HRR at the time of constant HR decay for the first 60 s of the recovery period (HR₆₀) was calculated as follows:

$$\text{HRR} = \text{HR}_{\text{peak}} - \text{HR}_{60}$$

Clinical characteristics

The clinical characteristics obtained from the patient medical records included age, sex, BMI, duration of HD, and dry body weight. The LV ejection fraction (EF), LV end-diastolic dimension (LVDd), and LV end-systolic dimension (LVDs) measured by echocardiography and blood samples (total protein, albumin, sodium, potassium, phosphate, calcium, hemoglobin, and hematocrit) were obtained before the day of CPX. Body weight at pre-HD (BW_{pre}) and post-HD (BW_{post}), body weight gain during the HD interval, body fluid removal, and body fluid removal rate were measured at each HD session, and the values for over 2 weeks were averaged.

Intradialytic blood pressure measurements

Intradialytic blood pressure was measured on the same arm in the supine position at 1-h intervals (at the start of dialysis and four times during dialysis: a total of five times in one HD session) using an automated sphygmomanometer over 2 weeks from the next HD session after CPX. The average SBP (SBP_{av}) was calculated over a total of 30 measurement times (five times during one HD session × three times/week × 2 weeks). In reference to several previously reported studies [4, 15, 16], we measured the number of times the SBPs became less than 100 mmHg over 2 weeks and recorded it as the blood pressure response.

Statistical analysis

All continuous data were summarized as means \pm SD and categorical data as numbers (%). The association between blood pressure instability (SBP_{av} and the number of times the SBPs became less than 100 mmHg over the 2 weeks) and exercise tolerance (VO_{2AT} , VO_{2peak} , $Load_{AT}$, and $Load_{peak}$), HRR, and cardiac function (EF, LVDd, LVDs), HD conditions (BW_{pre} , BW gain and gain rate of HD interval, fluid removal, ultrafiltration rate), laboratory data (total protein and albumin) were assessed. Either Pearson's or Spearman's correlation coefficients were used depending on whether variables were normally distributed or not. Coefficient values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS version 23.0 for Windows (IBM, Tokyo Japan).

Results

The demographic features, clinical laboratory variables, echocardiography variables, and usage of drugs by the subjects are shown in Table 1. The measured values of exercise tolerance (VO_{2AT} , VO_{2peak} , $Load_{AT}$, and $Load_{peak}$), HRR, HD condition (BW_{pre} , BW_{post} , body weight gain at HD interval, body fluid removal, and body fluid removal rate), and blood pressure response (SBP_{av} , number of patients with SBPs of less than 100 mmHg, and number of times the SBPs became less than 100 mmHg) are shown in Table 2. No serious hypotension, including symptomatic hypotension, requiring cessation of fluid removal or treatment with medication, was observed during this study.

The correlation coefficients between the blood pressure response and exercise tolerance, HRR, and cardiac function are presented in Table 3. The SBP_{av} that showed a significant correlation was $Load_{AT}$ ($r = 0.46$, $p < 0.05$) and $Load_{peak}$ ($r = 0.43$, $p < 0.05$). The relationship between the SBP_{av} and HRR was not significant ($r = 0.39$); however, there was a strong trend, with a p value of 0.06. The number of times the SBPs became less than 100 mmHg had a significant correlation with the HRR ($r = -0.44$, $p < 0.05$). No significant relationship between the HD conditions, the cardiac function measured by echocardiography, laboratory data, and the blood pressure response was observed.

Discussion

The main finding of this study is that exercise tolerance measured by the exertion of load at and peak exercise and the HRR are correlated with blood pressure response during HD in patients with no obvious hypotension. A previous study reported that for the examined relationship between the lowest intradialysis BP and mortality, after adjustment for known prognostic factors, the odds ratio for SBP between

Table 1 Subject characteristics

	Mean \pm SD
Age (year)	65.3 \pm 10.2
Sex (men/women)	12/11
Height (cm)	157.8 \pm 8.9
Dry weight (kg)	55.5 \pm 13.8
BMI (kg/m ²)	22.8 \pm 4.2
History of disorder (n (%))	
Diabetes	9 (39.1)
Hypertension	18 (78.2)
Angina pectoris	6 (26.1)
Hyperlipidemia	6 (26.1)
Laboratory data	
Total protein	6.9 \pm 0.7
Albumin	3.6 \pm 0.4
Sodium	136.8 \pm 3.7
Potassium	4.4 \pm 0.7
Phosphorus	5.2 \pm 0.9
Calcium	9.1 \pm 0.6
Hemoglobin	10.9 \pm 1.3
Hematocrit	33.6 \pm 4.1
Echocardiography	
EF (%)	66.4 \pm 11.7
LVDd (mm)	47.5 \pm 7
LVDs (mm)	29 \pm 6.6
Medicine (n (%))	
Calcium antagonist	10 (43.5)
ACE inhibitor	1 (4.3)
ARB	7 (30.4)
Amezinium metilsulfate	2 (8.8)
Droxidopa	1 (4.3)

ARB angiotensin II receptor blocker, EF ejection fraction, LVDs left ventricular end-systolic dimension, LVDd left ventricular end-diastolic dimension

110 and 119 mm Hg was significantly associated with mortality compared with 130–139 mmHg as a reference [4]. Additionally, a previous review on IDH showed that the highest mortality risks associated with IDH were observed when the intradialytic systolic blood pressure nadirs were < 90 and < 100 mmHg [16]. This study defined blood pressure instability as a low level of systolic blood pressure with ultrafiltration of hemodialysis, differing from previous studies that showed an obvious IDH. However, as previous studies have shown that low blood pressure levels are associated with a significantly worse prognosis, the indicator of < 100 mmHg pressure and average systolic blood pressure adopted in this study may have clinical significance as blood pressure instability.

Table 2 Exercise tolerance and HD condition

	Mean ± SD
Exercise tolerance	
VO _{2AT} (ml/min/kg)	9.3 ± 2.2
Load _{AT} (watt)	37.1 ± 9.8
VO _{2peak} (ml/min/kg)	12.8 ± 4.2
Load _{peak} (watt)	54.3 ± 19.5
HRR (bpm)	6.4 ± 6.1
HD condition	
BW _{pre} (kg)	57.1 ± 13.5
BW gain of HD interval (kg)	1.9 ± 0.7
BW gain of HD interval (%)	3.5 ± 1.2
Fluid removal (L)	2.1 ± 0.7
Ultrafiltration rate (L/h)	0.53 ± 0.16
Blood pressure response	
SBP _{av} (mmHg)	139.3 ± 22.5
Number of hypotension (SBP less than < 100 mmHg) (n)	
6 times	1
3 times	1
2 times	3
1 time	2
Total	7
Number of hypotension (SBP less than < 100 mmHg) (times/patient)	
	2.4 ± 1.7

AT anaerobic exercise threshold, HRR heart rate recovery, BW body weight, BW_{pre} body weight at before HD, BW_{post} body weight at after HD, SBP_{av} average systolic blood pressure over 6 times HD session

Table 3 Correlation between blood pressure response during HD and exercise tolerance or cardiac function

	R		Number of hypotension (SBP < 100 mmHg)	p
	SBP _{av}	p		
Age	- 0.39	n.s.	0.14	n.s.
BMI	0.13	n.s.	- 0.1	n.s.
BW gain of HD interval	0.35	n.s.	0.3	n.s.
Fluid removal	- 0.24	n.s.	0.29	n.s.
Ultrafiltration rate	- 0.23	n.s.	- 0.2	n.s.
Total protein	0.90	n.s.	0.32	n.s.
Albumin	0.33	n.s.	- 0.90	n.s.
EF	0.01	n.s.	0.16	n.s.
LVDd	0.19	n.s.	0.04	n.s.
LVDs	0.17	n.s.	0.25	n.s.
VO _{2AT}	0.22	n.s.	- 0.40	n.s.
Load _{AT}	0.46	< 0.05	- 0.22	n.s.
VO _{2peak}	0.17	n.s.	- 0.27	n.s.
Load _{peak}	0.43	< 0.05	- 0.22	n.s.
HRR	0.39	0.06	- 0.44	< 0.05

SBP_{av} average systolic blood pressure over 6 times HD session, AT anaerobic exercise threshold, HRR heart rate recovery, EF ejection fraction, LVDs, left ventricular end-systolic dimension, LVDd left ventricular end-diastolic dimension

The blood pressure response during HD is regulated by several mechanisms. It is well-demonstrated that acute hypotension observed during HD develops as a result of hypovolemia and inadequate compensatory mechanisms to counter the reduced intravascular volume [5, 13]. The Japanese clinical guidelines for the cardiovascular complications in HD patients [6] demonstrate that the cause of IDH is an inadequate dry weight setting, hypoalbuminemia that induces the reduction of the plasma refilling rate, reduced cardiac function, and abnormalities in the autonomic nervous system. A previous study has shown that ischemic heart disease and LV systolic dysfunction [17] were the main predictors of hemodynamic instability. However, the present study includes no uncontrolled patient who had severe LV dysfunction (EF of $66.4 \pm 11.7\%$, Table 1) and inadequate body weight gain (average weight gain including 2 days of HD interval of $3.5 \pm 1.2\%$, Table 2). Additionally, this study shows not only a correlation between the HD conditions and albumin levels, but also LV function and blood pressure responses during HD (Table 3). Previous studies have shown that the measures of LV performance obtained at rest did not accurately reflect exercise capacity in patients with chronic heart failure [18] and that changes in the EF at pre- to mid-dialysis periods, which do not reflect the absolute value of the EF, were significantly associated with IDH [19]. These studies suggested that the instability of blood flow was associated with not only the LV function at rest but also capabilities in dynamic regulation, such as compensation in the LV systolic function, VO_2 , and HR during exercise. Although the control of blood pressure during HD is a complex process resulting from the interaction of several mechanisms, these data suggest that blood perfusion instability is associated with exercise intolerance and an autonomic nervous system response.

HD patients demonstrate a severely impaired capacity for physical work and exercise tolerance, which has been reported to be as low as 50–60% of that measured in healthy subjects [8, 9]; the VO_{2peak} of the subjects in the present study was 12.8 ± 4.2 mL/min/kg (Table 2), which is lower than the predictive value for survival, i.e., 17.5 mL/min/kg [20]. Moreover, this study showed that the low exercise tolerance in the HD patients was associated with blood pressure instability over 2 weeks of HD. The blood pressure response is related through various nervous system mechanisms related to the sympathetic nervous system, vasoconstriction, and baroreflex activity. Previous studies have shown that baroreflex sensitivity regulates blood pressure by sensing changes in blood pressure and that a negative feedback [21] has an inverse relationship with exercise tolerance [22]. Additionally, autonomic dysfunction measured by HR variability in

HD patients was significantly correlated with exercise intolerance during the exercise treadmill test [23]. These studies suggested that exercise intolerance may affect blood pressure instability during HD through inactivity of baroreflex sensitivity and autonomic function.

Autonomic dysfunction is highly prevalent in HD patients [24] and has been implicated in the increased risk of blood pressure instability during HD [17, 25]. Indeed, this study showed that the HRR, which reflects parasympathetic activation, was associated with blood pressure instability during HD. The HRR also reflects cardiac parasympathetic activation both in healthy individuals and patients with chronic conditions [26, 27], and HD patients have lower HRRs than healthy control subjects [28]. In 2286 healthy subjects, the HRR showed a significant correlation with exercise tolerance and resting SBP [7]. Additionally, a previous study has shown that patients with IDH demonstrated no significant change in the HR and sympathetic nerve activity as a compensatory response of hypotension and that autonomic dysfunction and increased arterial stiffness contributed to the vascular malfunction in HD patients [13].

Blood pressure instability was associated with exercise load at and peak, not VO_2 . However, the mechanism behind such is unknown. A previous study has demonstrated that the skeletal muscular mass affects autonomic function [29]. HD patients have a low muscular mass [30] and poor muscular strength [31] in addition to exercise tolerance evaluated by VO_2 [8, 9]. The exercise load might reflect the autonomic activity and blood pressure response better than VO_2 because the former might be an index that could assess exercise tolerance, muscular mass, and muscular strength complexity. Further studies are required to further investigate the relationship between exercise tolerance and the blood pressure response during HD.

This study has some limitations. Firstly, this study was based on stable HD patients, not patients with severe IDH episodes. Patients with IDH who have dialysis problems may have different exercise tolerance and blood pressure responses. Secondly, this study has a small sample size; thus, it has not fully excluded confounding factors and could not further elucidate significant factors in multivariate analysis. We have to adjust for the effect of body fluid control measured by body impedance analysis and the influence of intra and/or extra dialytic drugs, diabetes, and sex. In this study, most patients use drugs that affect blood pressure. As this study cannot verify the effects of different drugs, future studies are necessary. The included ratio of diabetic patients of this study is similar to the results of a survey by the Japanese Society for Dialysis Therapy that the ratio of diabetic nephropathy patients was 43.7%. This study cannot adjust for the confounding factor of diabetes, but may be close

to the population of Japanese dialysis patients. Further studies are required to investigate the relationship between exercise tolerance and the blood pressure response by adjusting for these variables.

Conclusion

This study investigates the association between the blood pressure response during HD and exercise tolerance or the HRR, which reflects autonomic function. Blood pressure instability during HD is significantly associated with exercise tolerance and the HRR measured using CPX. Exercise intolerance in HD patients may be associated with blood pressure instability through autonomic dysfunction.

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Authors' contributions

HY conceived the study, participated in its design and coordination, and wrote the first draft of the manuscript. KK participated in the design of the study and performed the statistical analyses. KK, RS, and AM measured the data of this study. YM integrated the research data measurements as the measurement manager. HK treated the patients and measured the clinical data as the principal doctor. All authors read and approved the final manuscript.

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Availability of data and materials

Please contact author for data requests.

Ethics approval and consent to participate

This study conformed to the provisions of the Declaration of Helsinki, and written informed consent was obtained from all participants. The study was approved by the Nagoya Kyoritsu Hospital Ethical Committee (K118-02).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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