IMPACT OF DIASTOLIC DYSFUNCTION ON PHYSICAL FUNCTION AND BODY COMPOSITION IN MAINTENANCE HEMODIALYSIS PATIENTS

BY

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THESIS

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ABSTRACT

Background: Cardiovascular (CV) complications are the main cause of death in maintenance hemodialysis (MHD) patients. Although metrics related to left ventricular systolic dysfunction (LVSD) such as ejection fraction (EF) are commonly used to predict adverse CV outcomes, LV diastolic dysfunction (LVDD) measures may provide better prognostic values in MHD patients because they are less sensitive to blood volume changes. Additionally, muscle wasting and declines in physical function are common in MHD patients. This can result from abnormalities in cardiac function, which can be further worsened by physical deconditioning. Little is known about the relationship between cardiac function and physical function in MHD patients.

Aim: To evaluate the prevalence of LVDD and to assess its relationship to physical function and body composition in patients undergoing MHD.

Methods: Walking performance, leg strength, and whole body lean mass (WBLM) by DXA were measured in 83 MHD patients (age=54.4± 12yr). Echocardiography was used to assess LVSD measured by EF and LVDD evaluated by mitral inflow velocity (E), peak late mitral inflow velocity(A), peak early diastolic mitral annular velocity(E') and deceleration time of E (DT). We classified LVDD into: 1) mild DD (E/A< 0.8, E' <8 (cm/s), E/E'<8, and DT <200ms) and 2) advanced DD (E/A>0.8, E'<8(cm/s), E/E' >9, and DT <200ms).

Results: The prevalence of LVDD was 48.2% (14.5% with mild DD and 33.7% with advanced DD) and the prevalence of LVSD (EF < 40%) was 14.5%. 50% of patients with LVSD also had LVDD. BMI was significantly higher in patients with LVDD (p=0.016). Gait speed, shuttle walk test, leg flexion and extension strength, and WBLM% were significantly higher in the group without LVDD than with LVDD (p=0.005, 0.007, 0.041, 0.031 and 0.002; respectively). However, there was no significant difference in any measure of physical function or body composition between patients with and without LVSD.

Conclusion: This data indicates that LVDD is more closely related to physical function and body composition than LVSD in MHD patients, and suggests that LVDD may be an important therapeutic target.

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CHAPTER 1

INTRODUCTION

The prevalence of cardiovascular (CV) disease and CV mortality are excessively high in patients undergoing maintenance hemodialysis (MHD) therapy[1][2]. Cardiac abnormalities such as left ventricular (LV) hypertrophy, and systolic and diastolic dysfunction are present in up to 80% of MHD patients[3,4]. These cardiac abnormalities independently predict adverse cardiac events, and are the strongest predictor of mortality in this population[5,6].

It is well established that systolic dysfunction adversely impacts physical function; however, the relationship between diastolic dysfunction and physical function is not well characterized. LV diastolic dysfunction (LVDD), characterized by impaired LV dilation, is strongly associated with poor exercise capacity in cardiac patients[7-9]. The exact mechanism for this is unclear, but possible explanations may include inadequate cardiac output and exertional dyspnea. During exercise, an increase in LV diastolic filling ensures an adequate cardiac output, while failure to increase cardiac output sufficiently under high demands can limit physical performance. Additionally, an increased LV filling pressure, a main feature in advanced LVDD, induces an increased pulmonary capillary pressure which may cause exertional dyspnea[10]. In MHD patients, declines in physical function are very common and significantly impair a patient's quality of life (QOL) [11-15]. A variety of noncardiac-factors, such as decreased muscle mass[16,17], abnormal muscle metabolism[18-21], and inflammation, are known to contribute to low physical function in HD patients[12,13,22,23]. However, very few studies have examined the relationship between cardiac function and physical function in HD patients [12,24][25], and no studies to date have examined the specific contribution of LVDD on reduced physical functioning in HD patients.

Although measures of LV systolic function such as ejection fraction (EF) are commonly used to predict adverse CV outcomes in various populations, the influence of loading condition may

substantially limit accurate assessment of cardiac function in MHD patients. For example, accumulation of fluid volume may drive an increased EF which could be falsely interpreted as an improvement in myocardial contractility. LV diastolic function measures have been proposed to provide better prognostic values in this population because they are less sensitive to blood volume changes than systolic function measures[26-28]. Furthermore, LV diastolic function parameters were shown to be a better predictor of exercise capacity than systolic measures in 2,867 individuals referred for exercise echocardiography examinations[29], and also in cardiac patients[30, 31].

Therefore, the purpose of this study was to evaluate the prevalence of LVDD and to assess the relationship between LVDD and physical function in patients undergoing MHD. We hypothesized that worsened LV diastolic function will be associated with declines in physical function in MHD patients.

CHAPTER 2

RESEARCH DESIGN AND METHODS

Study population

Eighty three patients receiving thrice weekly MHD therapy were recruited from dialysis clinics in Champaign, IL and Oak Park, IL. Patients were screened for eligibility with a health and medical history questionnaire. All participants provided written informed consent and this study was approved by the University of Illinois Institutional Review Board. Inclusion criteria for participation in this study included the following: 1) patients on MHD treatment >3 months; 2) an age of 30-70 years; 3) at least 3 days of HD treatments per week; 4) medical clearance from a nephrologist. Subjects were excluded if they had chronic obstructive pulmonary disease (COPD), decompensated congestive heart failure (CHF), or cardiovascular surgery (e.g., coronary bypass, valve replacement, or angioplasty) in the past 6 months.

Echocardiography

The transthoracic echocardiographic examinations were performed using a high resolution ultrasound system (ProSound SSD-α7, Aloka, Japan). The measurement sessions occurred 24 hours after an HD session on a non-dialysis day to minimize the effect of fluid overload. Two-dimensional images were obtained according to the recommendations of the American Society of Echocardiography[32]. At least 3 consecutive heartbeats in each view were acquired. LV volumes and LV mass were measured in M-mode using the Teicholz method. LV volume parameters were indexed by body surface area (BSA). LVSD was defined as an LV EF < 40%. Left ventricular mass index (LVMI) was calculated as $LVM/height^{2.7}$. LV diastolic function was assessed by standard Doppler echocardiographic indices [33-35]. LV diastolic filling patterns were assessed by placing the pulsed Doppler sample volume between the tips of the mitral valve leaflets. Based on the mitral

inflow velocity curve, peak E velocity (E), its deceleration time (DT), peak A velocity (A), and E/A ratio were assessed. In addition, the ratio of early mitral inflow velocity to peak mitral annulus velocity (E/E' ratio) was measured using Tissue Doppler imaging of mitral annulus movement. We graded LV DD stages according to the guidelines from the EAE/ASE using an integrated evaluation of LV filling patterns [36] : 1) mild DD ; impaired relaxation (E/A < 0.8 , E' <8 cm/s, E/E' < 8 and DT > 200ms), 2) moderate DD; pseudo normal filling (0.8< E/A< 2, E' <8 , E/E'<9, and DT <200) and 3) severe DD; restrictive filling (E/A>2, E'<8, E/E' >9, and DT <200).

Shuttle Walk Test and Gait Speed Assessment

An incremental shuttle walk test (ISWT) was conducted to estimate cardiorespiratory performance[37]. ISWT is a progressive test in which patients walk back and forth continuously over a 10 meter course. The walking speed is paced by a series of beeps that signal when the subject should have completed the 10 meter walk. The pace is progressively increased so that the walking speed at the end of each successive minute is ≥ to: 1.12, 1.54, 1.88, 2.26, 2.64, 3.02, 3.4, 3.78 miles per hour. The test was terminated when the subject was unable to complete the 10m course before the subsequent beep.

Normal gait speed was measured prior to the start of the ISWT while patients walked at a self-selected speed along a 10-meter walkway with time recorded. Average gait speed was calculated based on 3 trials. These walking tests were performed on non-dialysis days, 18 to 30 hours after a previous dialysis session.

Muscle Strength

Bilateral quadriceps femoris and hamstring muscle strength was evaluated using isokinetic testing modes. Following dynamometer calibration, knee extension, and flexion isokinetic peak muscle torque (Nm) was evaluated at a speed of 60 degrees per second on a Biodex System 3

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dynamometer (Biodex Medical Systems, Shirley, NY). The axis of rotation of the machine was aligned with the lateral epicondyle of the femur. The calf pad was positioned halfway between the lateral malleolus of the fibula and lateral epicondyle of the femur, and securely attached to the subject using straps. Straps were placed over the thighs, pelvis, and torso regions to minimize movement during the test. Participants performed two sets of 6 repetitions, with a 3-minute rest between sets, and the best effort was used for analysis. For all tests, participants were verbally encouraged to perform as vigorously as possible.

Body Composition

Whole body fat, lean and bone mass were measured by dual emission x-ray absorptiometry (DXA, Hologic QDR 4500A, Bedford, MA). Whole body and regional mineral free lean mass was calculated by subtracting the bone mineral content from the lean mass quantity of the whole body or region of interest. Whole body bone mineral density (WBBMD) was also measured. Precision for DXA measurements of interest are ~1.0 – 2.0% in our laboratory.

Statistics Analysis

Continuous data were expressed as mean ± standard deviation and compared using independent samples t-test. Categorical data were displayed as frequencies and percentages, and compared using χ^2 tests or Fisher exact tests as appropriate. Correlations between continuous variables were analyzed using Pearson's correlation test. All statistical analysis was two sided. A p-value lower than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 15.0 statistic software.

CHAPTER 3

RESULTS

Subject Characteristics and Prevalence of LV Diastolic and Systolic Dysfunction

Eighty three MHD patients were included in the analysis. Patient demographics are shown in *Table 1*. The prevalence of LVDD was 48.2% (33.7% with moderate and severe LVDD and 14.5% with mild LVDD). There were no significant differences in age, diabetes status and smoking status between groups with and without LVDD. The group with LVDD had a higher percentage of females and higher BMI than the non-LVDD group. LVSD was identified with 10 patients (14.5%), and there was no difference in all demographics parameters between groups with and without LVSD. LVSD was identified in 12.5% of patients in the LVDD group and 11.6% in the non-LVDD group.

Body composition and LVDD

WBLM%, left and right leg LM % were significantly lower, and trunk fat % was significantly higher in the group with LVDD than without LVDD. There was no difference in WBBMD between LVDD and non-LVDD groups (Table 1). There was no difference in body composition parameters between groups with and without LVSD.

Physical function and LVDD

Patients with LVDD had a significantly slower gait speed and worse performance on the ISWT and leg maximal extension and flexion than the group without LVDD (Table 2). There was no difference in physical function performance between groups with and without LVSD.

CV parameters and LVDD

There was no difference in blood pressure or echocardiographic parameters, with the exception of E' and E/E', between groups with and without LVDD (Table 2). Due to the body size difference (BMI) between groups with and without LVDD, SV and CO were indexed by BSA and compared. There was no difference in SV index (SVI) and CO index (COI) between groups (SVI: 25.76 ± 13.22 vs 31.01 ± 15.61, p=.117 and COI: 2.17 ± 1.1 vs 2.24 ± 1.46, p=0.845). Comparing groups with and without LVSD, there was no difference in blood pressure or echocardiographic parameters, with the exception of ESV (82.34 ± 28.55 vs 39.22 ± 4.90, p=0.002), CO (1.96 ± 0.92 vs 4.66 ± 2.65, p<0.001), SV (23.90 ± 11.32 vs 60.97 ± 28.23, p=0.004) and EF (23.65 ± 10.88 vs 63.67 ± 12.93, p<0.001).

Table 1: Subject Characteristics

	Total[a]	Patients with LVDD[a]	Patients without LVDD[a]	p-value[b]
Patient Number	83	40	43	
Gender (male,%)	49 (59%)	17 (42.5%)	32 (74.4%)	**0.003**
Age (y)	54.4 ± 12	53.7 ± 12.3	55 ± 11.7	0.605
BMI (kg/m^2)	31.6 ± 7.2	33.5 ± 7.6	29.8 ± 6.4	**0.016**
WBLM (%)	66.3 ± 10.5	62.6 ± 9.0	69.6 ± 10.7	**0.002**
Trunk fat (%)	31.6 ±11.2	35.2 ±10.1	28.4 ± 11.1	**0.005**
Right leg LM (%)	68.2 ± 11.0	64.5 ± 10.4	71.6 ± 10.5	**0.002**
Left leg LM (%)	68.2 ± 10.8	64.3 ± 10.2	71.6 ± 10.1	**0.002**
WBBMD (g/cm^2)	1.1± 0.2	1.0 ±0.1	1.1 ± 0.2	0.488
Smoking status (n, %)	24 (28.9%)	8 (20%)	16 (37.2%)	0.084
Diabetes (n, %)	40 (48.2%)	21(52.5%)	19 (44.2%)	0.449

a: Data expressed as mean ± SEM for continuous variables and numbers for countable variables
b: p-value for group difference between patients with and without LVDD
BMI = body mass index, **ESRD** =end-stage renal disease, **WBLM** = whole body lean mass, **LM** = lean mass, **WBBMD** = whole body bone mineral density.

Table 2: Physical and Cardiac Function Parameters

	Total[a]	Patients with LVDD (N=40)[a]	Patients without LVDD (N=43)[a]	p-value[b]
ISWT (sec)	227 ±134.8	217.8 ± 105.1	289.5 ± 122.3	**0.007**
Gate speed (m/sec)	0.88 ± 0.27	0.80 ± 0.28	0.97 ± 0.24	**0.005**
Peak torque extension (Nm)	81.4 ± 38.9	71.5 ± 31.1	90.6 ± 43.2	**0.031**
Peak torque flexion (Nm)	39.4 ± 20.5	34.5 ± 16.5	44.0 ± 22.8	**0.041**
SBP (mmHg)	134.4 ± 28	133.2 ± 32.1	135.6 ± 24.1	0.721
DBP (mmHg)	75.3 ± 16.9	74.4 ± 19	76.3 ± 14.8	0.622
EDV(mL)	101.7 ± 54.6	92.9 ± 42.3	109.6 ± 63.2	0.19
ESV (mL)	45.5 ± 40.5	40.9± 34.5	49.5 ± 45.3	0.367
SV(mL)	56.1 ± 29.4	50.7 ± 26	61.2 ± 31.7	0.115
CO (L)	4.3 ± 2.7	4.2 ± 2.9	4.4 ± 2.8	0.838
EF (%)	58.8 ± 18.2	58.4 ± 19.7	59.1 ± 17	0.868
LVIDd (cm)	4.6 ± 1	4.3 ± 1.3	4.4 ± 1.5	0.889
IVSd (cm)	1.7 ± 0.5	1.74 ± 0.5	1.6 ± 0.5	0.19
LVPWd(cm)	1.8 ± 0.8	1.9 ± 0.9	1.8 ± 0.7	0.672
LVMI (g/m$^{2.7}$)	73.2 ± 43	75.8 ± 40.8	76 ± 42.3	0.9
LVH (n)	72	34	38	0.11
E/A	1 ± 0.4	1.1 ± 0.5	1.04 ± 0.3	0.345
S'(cm/s)	10.7 ± 11.1	11 ± 15.8	10.5 ± 4	0.834
E' (cm/s)	11 ± 4.9	8.8 ± 3.9	12.9 ±4.9	**0.000**
A'(cm/s)	11.6 ± 4.8	10.5 ± 4	12.5 ± 5.2	0.064
E/E'	7.6 ± 4.2	10.1 ± 4.8	5.5 ± 2.3	**0.000**
DecT of E (ms)	165 ± 74.8	157.1 ± 63	172.5 ± 84.4	0.352
A duration	144 ± 78.8	134.2 ±85.9	152.8 ± 71.7	0.294
LVSD (n)	10	5	5	

a: Data expressed as mean ± SEM for continuous values and a number for countable values.
b: p-value for group differences between patients with and without LV DD, **ISWT** = incremental shuttle walk test, **SBP** = resting brachial systolic blood pressure, **DBP**= resting brachial diastolic blood pressure, **EDV**=end diastolic volume, **ESV**=end systolic volume, **SV**= stroke volume, **CO**= cardiac output, **EF**= ejection fration, **LVIDd**= left ventricular interdiameter at diastolie, **IVSd**=interventricular septum thickness at diastole, **LVPWd**= left ventricular posterior wall thickness at diastole, **LVMI**: left ventricular mass index; LVM/height$^{2.7}$, **LVH**= left ventricular hypertrophy, **E/A**= the ratio of early / late diastolic mitral valve flow velocity, **DecT of E**= deceleration time of early diastolic mitral valve flow (E), **LVSD**: left ventricular systolic dysfunction.

CHAPTER 4

DISCUSSION

The primary findings of our study include the following: 1) the prevalence of LVDD was significantly higher than LVSD; 2) measures of physical function (gait speed) and physical performance (ISWT and leg strength) were lower in those with LVDD; and 3) those with LVDD had a reduced whole body and leg LM% and higher trunk fat% in MHD patients without major CV complications. Our findings suggest that impaired LVDD may be an important mediator of declines in physical performance and body composition in MHD patients. To our knowledge, this is the first study to analyze the relationship between LVDD, physical performance and body composition in MHD patients.

Prevalence of Cardiac Abnormalities in MHD Patients

Our echocardiographic data shows that approximately half of MHD patients had LVDD while the prevalence of LVSD was much lower (15%). It is well established that LVSD measures are volume dependent. Because our ultrasound assessments were conducted on a non-dialysis day, fluid accumulation over the previous 24 hours may have artificially lowered the prevalence of LVSD in our patients. Other studies reported a similar incidence of LVDD (50-75%) and LVSD (10~40 %) in MHD patients including those with CHF[38,39, 40]. It should be noted that our analysis excluded patients with decompensated CHF. CHF can be caused by LVSD, LVDD, or both, but LVSD, identified by a decreased EF, is commonly used as a useful echocardiographic diagnostic for CHF. This may explain the relatively low LVSD prevalence in our analysis. Early and accurate CHF diagnosis is challenging due to non-specific physical symptoms and various comorbidities[41-43]. Furthermore, a lack of knowledge about diagnosis of diastolic CHF (CHF with preserved EF) may complicate CHF diagnosis[44, 45]. Protocols for diagnosing CHF have changed little in the past decade,

and evidence suggests the disease is often misdiagnosed[46, 47]. Thus, our finding that there is a relatively high prevalence of LVDD in patients without decompensated CHF, suggests an under-detection of cardiac dysfunction by regular clinical screenings in this population. LVH, a surrogate for myocardial structural abnormalities, was identified in 83.7% of patients in our analysis which is consistent with previous findings in MHD patients[48-50]. This high LVH prevalence suggests that LV structural remodeling occurs frequently before developing cardiac dysfunction regardless of the presence of decompensated CHF in MHD patients. Indeed, LVH is known to initiate a vicious cycle of cardiac maladaptation in MHD patients[51-53]. Together with accompanying interstitial fibrosis and myocardial ischemia, increases in LV mass contributes to impaired LV diastolic distensibility, a main feature of LVDD. As LVDD progresses, LV end-diastolic pressure increases as a consequence of inadequate LV filling in response to given change in blood volume. Therefore, patients with LVDD may suffer from CV complications due to a noncompliant myocardium, i.e., an inability to change LV volume for a given change in pressure. This results in either pulmonary congestion with an increased blood volume or hypotension with a decreased blood volume. This has significant clinical implications for MHD patients who experience frequent blood volume shifts between MHD treatments and during a MHD treatment. Therefore, identification of LVDD would provide important information for therapeutic strategies to prevent adverse CV events in MHD patients.

One interesting finding is that there was a higher percentage of females in the LVDD group than in the non-LVDD group (57.5% vs 25.5% respectively, p=0.003). This high prevalence of LVDD in female dialysis patients may be explained by female hormone abnormalities. It is not surprising that both chronic uremia and renal replacement therapies may induce abnormal regulation of female hormones; thus, various female-hormone relating symptoms have been reported such as menstrual irregularities, anovulation, infertility, sexual dysfunction and early menopause in female ESRD patients[54]. In general, healthy young women have fewer CV complications than the age-matched men. However, female MHD patients have accelerated rates of CVD and mortality[55-57].

Although not accounted for in this study, hormonal factors may have contributed to the greater LVDD in women in this study.

Decreased Physical Function and Cardiac Abnormality in MHD Patients

Growing evidence suggests that patients on MHD treatment experience reduced physical functioning, which is associated with a poor prognosis and impaired quality of life[14, 58, 59]. Exercise capacity has been shown to be ~50% of the level in healthy sedentary control[11, 12, 14], and the actual average is thought to be lower because patients who were unable to perform certain exercise tests were excluded from the analysis. A combination of clinical factors likely interacts to reduce exercise capacity in MHD patients. These include 1) chronic uremia-related factors such as hypertension, metabolic disturbances, anemia and muscle wasting, 2) MHD treatment-related factors such as ischemia, acute inflammation, and physical inactivity during dialysis treatments, 3) psychological-related factors such as depression and 4) low chronic levels of physical activity[11, 13, 14, 60-62].

Many of these factors are closely related to cardiac performance. Broadly speaking, exercise capacity is affected by the efficiency of oxygen delivery (central factors) and oxygen utilization (peripheral factors). In end-stage renal disease (ESRD) patients who are required to receive a renal replacement therapy such as MHD, impaired cardiac function[63] and poor muscle blood flow[64, 65] limit efficient oxygen supply, and decreased muscle mass[16, 17] and muscle metabolism[18-21] impairs peripheral oxygen utilization, both of which contribute to the reduced exercise capacity. Our study found that reduced physical function in MHD patients was associated with LVDD. Specifically, patients with LVDD had significantly slower gait speed, poorer performance on a shuttle walk test, and reduced hamstring and quadriceps strength. The possible pathophysiologic explanation for this association is that impaired LV diastolic function leads to limited LV filling resulting in a decreased cardiac output even with a preserved systolic function. Especially, during exercise, the failure to increase cardiac output in response to the increased need may significantly limit exercise

performance[29]. Additionally, an increased LV filling pressure, a hallmark of LVDD, frequently coincides with an augmented LA pressure and the consequent increased pulmonary capillary wedge pressure which, in turn, can lead to ventilation-perfusion abnormalities. These pulmonary abnormalities contribute to limited gas-exchange during exercise, generating various symptoms such as shortness of breath, chest pain and fatigue that can limit exercise capacity[10]. Respiratory muscle weakness, a cause for dyspnea and tachypnea, has also been shown to be closely related to LVDD[66]. Regarding strength, abnormal skeletal muscle metabolism, including impaired mitochondrial energy transfer and ATP production have been found in heart failure models, and may also partially explain the strength decline in patients with LVDD[67, 68].

Despite these possible pathophysiological mechanisms, there is a paucity of data linking LV diastolic function with physical performance in MHD patients. In fact, several previous studies demonstrated the relationship between cardiac dysfunction, mostly using LV systolic parameters, and exercise capacity in ESRD patients[24, 25, 63, 69]. Bullock et al., demonstrated that the presence of cardiac abnormalities measured by a combination of LVSD, LVDD and LVH parameters, were inversely related to exercise capacity in ESRD patients [63]. Two exercise training studies showed that increased cardiorespiratory capacity was associated with improved cardiac function, supporting the positive relationship between physical function and cardiac function in MHD patients[24, 69]. The present study demonstrates a direct association between LVDD and reduced physical function, suggesting a potential cardiac mechanism underlying declines in physical function, and conversely, a role for physical impairment in cardiac dysfunction in MHD patients. In this regard, our findings implicate possible bidirectional therapeutic approaches to alleviate the critical health issues, abnormal cardiac function and impaired physical function, and to eventually improve the overall health in MHD patients.

LVDD vs LVSD; Relationships with Exercise Capacity

In MHD patients, it has been suggested that LV diastolic performance may better reflect CV fitness than systolic function due to the volume dependence of LVSF measures[38, 70, 71]. Although physiological contribution of LV systolic function to physical performance has been studied widely, recent studies reported echocardiographic LV systolic function parameters were poor predictors of exercise capacity in patients with mild and severe cardiac disorders[29-31]. Studies demonstrated that LV diastolic function surrogates such as E', E/E' and left atrial volume were strongly associated with exercise capacity in cardiac patients[10, 72, 73 74, 75 76 77 78]. Our study found that only LVDD, not LVSD, had a significant discriminating power in physical function and body composition in MHD patients.

LV DD and Body Composition

We also found associations between body composition (whole body and regional LM %) and body size (BMI) and cardiac function in MHD patients. As body size increases, augmented blood volume is necessary to meet a high metabolic rate which can in turn create a burden for a malfunctioning heart. The concomitant fat and lean mass increases may act differently to accommodate the increased hemodynamic need. Kadassis et al. demonstrated that whole body fat mass was associated with unfavorable CV adaptations such as increased heart rate, increased blood pressure, vascular resistance, impaired LV contractility and LVH. By contrast, whole body lean mass was primarily related to preload determinants such as CO, SV and LVEDV[79, 80]. This indicates that fat accumulation may disturb cardiac function and structure through autonomic and humoral dysregulation such as increased sympathetic activation. On the other hand, elevated lean mass may increase cardiac output to supply the increased metabolic needs of muscle. As evidence of this, increases in whole body fat percent were found to be correlated with impaired arterial function and cardiac function[81] and increased CV risk[82]. Additionally, increased diastolic filling pressure, a surrogate for LVDD, was widely reported in obese people[83-86].

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Many previous studies demonstrated a survival advantage with increasing BMI – called 'the obesity paradox" or "reverse epidemiology"[87-89], whereas some others found a positive relationship between BMI and all-cause mortality in dialysis patients[90, 91]. The link between high BMI and improved nutrition status may explain the obesity paradox because malnutrition status significantly contributes to high morbidity and mortality in HD patients[92, 93]. On the other hand, the unfavorable effect of high BMI on mortality was demonstrated when body sizes were assessed separately as lean mass and fat mass to further stratify wasting symptoms. For example, a high BMI with a low ratio of lean mass to fat mass, called sarcopenic obesity, was associated with increased inflammation levels and high mortality rates in MHD patients[91]. Apart from mortality data, little is known about the contribution of increased body size, even less with fat or lean masses, and cardiac function in MHD patients. In the present study, patients with LVDD had a higher BMI and lower WBLM% than the group without LVDD. Also, decreasing WBLM% was significantly correlated with worse walking capacity (p <0.001, data not shown), but this trend was not significant after controlling for body weight in our analysis. Indeed, lean mass is suggested to predict exercise capacity better than total body weight in the general population[94]. Taken together, our findings suggest body fat and lean mass should be used to further refine stratification of CV risk in relation to cardiac dysfunction in clinical settings in MHD patients.

Strengths and Limitations

This is the first study to our knowledge that assessed the association between LV diastolic function and functional capacity in MHD patients. Our analysis excluded patients with CV complications that are known to limit physical function such as CHF, COPD or cardiovascular surgery (e.g., coronary bypass, valve replacement, or angioplasty) in the past 6 months; therefore, the accuracy of predictability of LVDD on physical performance is not confounded by common CV-comorbidities. However, these exclusions may limit application of our findings to the general MHD

patients. Also, selection bias may exist for a possible overestimation of physical fitness in MHD patients.

The major limitation of our study is the possible inaccuracy of LVDD classification. Identification of LVDD is inherently difficult, and no simple noninvasive technique exists, unlike it does for LVSD diagnosis (LV EF <40%). LV end-diastolic filling pressure measures are proposed as standard diagnosing metrics, and echocardiographic Doppler technique is widely validated for diastolic functional measures[36, 95]. The most validated technique to estimate LV filling pressures, invasive catheters, was not used, and other possible contributors to affect LV diastolic function such as LA volume and filling profiles and arterial stiffness parameters were not available in this study. However, integrated indices using echocardiographic Pulse-Wave and Tissue Doppler assessments that our study used are widely validated to estimate LV filling pressure for LVDD classification, and their subclinical prognostic values have been well confirmed in patients with ESRD [27, 38, 71, 96]. Additionally, the design was cross-sectional, making a causal relationship impossible.

CHAPTER 5

CONCLUSIONS

The prevalence of LVDD was higher than LVSD in MHD patients without major CV complications such as CHF. The severity of LVDD, but not LVSD, was related to functional capacity and body composition in this population. Therefore, improvement of diastolic properties may be a therapeutic target to not only reduces CV disease risk but also to enhance physical functional capacity in MHD patients; conversely, enhanced physical function status may allow for improved LV diastolic function. Also, examining body composition by body fat and lean mass may improve CV risk stratification in relation to cardiac dysfunction. Further investigation is needed to confirm these findings, including in MHD patients with diagnosed CV comorbidities.

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