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Long-term Hemodialysis Corrects Left Ventricular Dyssynchrony in End-stage Renal Disease: A Study with Gated Technetium-99m Sestamibi Myocardial Perfusion Single-photon Emission Computed Tomography

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Introduction: Left ventricular (LV) dyssynchrony is common in patients with end-stage renal disease (ESRD), and echocardiographic assessment has shown that it can be improved by a single session of hemodialysis (HD). The aim of this study was to assess the effects of chronic HD on LV dyssynchrony in patients ESRD by means of gated technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography (GSPECT) with phase analysis.

Materials and Methods: Twelve patients with ESRD underwent GSPECT and echocardiography before the start of long-term HD (baseline) and 3 months later. In addition, 7 control subjects matched for age and sex underwent GSPECT and echocardiography within a 2-month period. To evaluate LV dyssynchrony, both histogram bandwidth (HBW) and phase standard deviation (PSD) were determined with phase analysis of GSPECT images. The end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction were also measured with GSPECT, and the LV mass index (LVMI) was measured with echocardiography. The LV dyssynchrony, volume, function, and mass were compared among control subjects, patients with ESRD at baseline, and patients with ESRD after 3 months of chronic HD.

Results: The LV dyssynchrony, volume, and mass at baseline were significantly greater in patients with ESRD than in control subjects (HBW, 65.5°±54.4° vs. 22.3°±7.5°, P<0.05; PSD, 21.0°±15.5° vs. 7.6°±5.5°, P<0.05; EDV, 105.7±29.2 vs. 72.3±13.9 mL, P<0.05; ESV, 44.3±22.1 vs. 20.9±10.3 mL, P<0.05; LVMI, 136.5±48.3 vs. 65.4±5.6 g/m^2, P<0.01). From baseline to the third month of chronic HD, there were significant increases in EDV (78.6±25.4 vs. 105.7±29.2 mL, P<0.01) and ESV (27.6±16.2 vs. 44.3±22.1 mL, P<0.01) and significant decreases in HBW (65.5°±54.4° vs. 31.0°±15.7°, P<0.01) and PSD (21.0°±15.5° vs. 10.0°±8.2°, P<0.01).

Conclusion: Chronic HD decreased LV dyssynchrony and volume in patients with ESRD. Serial phase analysis of GSPECT images is a useful method of assessing the effects of long-term HD on LV dyssynchrony and volume in patients with ESRD. (J Nippon Med Sch 2015; 82: 76–83)

Key words: left ventricular dyssynchrony, phase analysis, gated technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography, end-stage renal disease, chronic hemodialysis

Introduction

Chronic kidney disease is an important risk factor for cardiovascular disease[1], especially in patients with end-stage renal disease (ESRD) requiring hemodialysis (HD).

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In these patients, cardiovascular mortality is 10 to 20 times as great as that for persons in the general population matched for age and sex[2] and is closely related to cardiac alterations, including left ventricular (LV) hypertrophy, LV dysfunction[3], and LV dyssynchrony[4,5]. In particular, LV dyssynchrony is an important predictor of the response of severe refractory heart failure to cardiac resynchronization therapy (CRT)[6,7]. However, LV dyssynchrony is also prevalent in patients with ESRD[4,5,8–11].

Although LV dyssynchrony is most often assessed with echocardiography, which is noninvasive and easily performed, comparable results have been obtained with phase analysis of the cardiac cycle with gated technetium-99m (Tc-99m) sestamibi myocardial perfusion single-photon emission computed tomography (GSPECT)[12]. Measurements of LV dyssynchrony obtained by phase analysis with GSPECT correlate well with assessments made with tissue Doppler imaging[13]. Furthermore, treating ESRD with a single session of HD improves LV dyssynchrony, as assessed with echocardiography using tissue synchronization imaging and speckle-tracking strain imaging[8,9]. However, the effects on LV dyssynchrony of 3 months of HD have not been assessed, with either echocardiography or GSPECT with phase analysis.

Therefore, in the present study we used GSPECT with phase analysis to assess the effects of 3 months of HD on LV dyssynchrony in patients with ESRD.

Materials and Methods

Study Population

The study population was selected from among 16 consecutive patients with ESRD requiring long-term HD (10 men and 6 women; mean age, 63±14 years) who underwent GSPECT with phase analysis from January 2007 through December 2009. In addition, 7 matched control subjects (5 men and 2 women; mean age, 60±13 years), whose sex, age, and clinical background corresponded to those of patients with ESRD, were retrospectively selected from among 177 patients without signs of structural heart disease who underwent GSPECT with phase analysis during the same period. Patients with ESRD were excluded if they had acute coronary syndrome, atrial fibrillation, left bundle branch block, ventricular arrhythmia, severe valvular disease, or resting myocardial perfusion ischemia (summed rest score [SRS] ≥4) or if GSPECT images were too poor to interpret easily; therefore, the final study population included 12 patients requiring long-term HD (7 men and 5 women; mean age, 60±13 years).

To assess the effects of long-term HD, changes in GSPECT and echocardiographic data were compared from baseline (before the start of HD) to approximately 3 months after the start of HD. All GSPECT scans, including phase analysis, and echocardiographic observations were performed the day before an HD session. The mean interval between assessments was 101 days (range, 90–128 days).

This study was approved by the ethics committee of Nippon Medical School Musashikosugi Hospital, and all patients with ESRD gave informed consent to participation. In addition, the 7 control subjects gave written permission for the use of their data.

Hemodialysis

All patients underwent HD treatment 3 times per week with polysulfone dialyzers. Blood flow was usually 150 to 200 mL/min, with a constant dialysate flow rate of 500 mL/min. The ultrafiltration rate varied to achieve the patient's clinically determined "dry weight."

Biochemical Analyses

Plasma levels of hemoglobin, albumin, urea, creatinine, calcium, phosphate, intact parathyroid hormone, high-sensitivity C-reactive protein (hsCRP), and brain natriuretic peptide (BNP) were measured using routine methods at baseline and after 3 months of HD.

Echocardiography

All patients were examined with conventional 2-dimensional echocardiography and tissue Doppler imaging using the Vivid 7 cardiovascular ultrasound system (GE Healthcare, Little Chalfont, UK) equipped with a multifrequency transducer. All echocardiographic data were analyzed according to the guidelines of the American Society of Echocardiography. The LV ejection fraction (LVEF) was calculated on the basis of apical 2- and 4-chamber views using the modified Simpson's rule. The LV mass index (LVMI), an indicator of LV structural integrity, was calculated by dividing LV mass by body surface area, according to American Society of Echocardiography guidelines[14].

GSPECT Imaging

All subjects underwent resting GSPECT. A dose of approximately 740 MBq of Tc-99m sestamibi was administered intravenously with the subject at rest. Resting GSPECT image acquisition was started 40 minutes later. A dual-head gamma camera with a fixed 180° angle between heads (Toshiba, Tokyo, Japan), equipped with low-energy, high-resolution collimators, was used for all GSPECT imaging. An energy pulse height analysis win-

dow of ±10% was centered over the 140-keV Tc-99m photo peak. Projection data were acquired with a total of 60 stops (step and shoot mode, 40 seconds/stop) over a 180° orbit for each detector. The GSPECT images were reconstructed with the filtered back projection method using a Butterworth filter (order 8; cut-off, 0.55 cycle/cm). Images were gated at 16 frames per resting cardiac cycle. All images were acquired using an image matrix of 64× 64 pixels.

To determine the presence of resting myocardial ischemia, semiautomated quantitative 17-segment visual interpretation was performed with quantitative myocardial perfusion SPECT (abbreviated as QPS), a software program developed by Cedars-Sinai Medical Center (Los Angeles, CA, USA), using the standard 5-point scoring system (0, normal; 1, slightly reduced uptake; 2, moderately reduced uptake; 3, severely reduced uptake; 4, no uptake) of the American College of Cardiology and the American Society of Nuclear Cardiology[15]. The SRS was obtained by combining the scores for each of the 17 segments of the resting GSPECT images. Resting ischemia was defined as SRS ≥4 without attenuation artifacts. The GSPECT images were evaluated randomly by expert observers who were blinded to subjects' clinical history and electrocardiographic findings.

Quantitative Analysis of LV Volume and Function

The LV end-diastolic volume (EDV), end-systolic volume (ESV), and the LVEF were determined by analyzing GSPECT images with quantitative gated SPECT (abbreviated as QGS), a software program developed by Cedars-Sinai Medical Center[16].

Evaluation of LV Dyssynchrony with Phase Analysis of GSPECT Images

Gated short-axis images were segmented with QGS, which can be used to determine the values of new global and regional quantitative variables for assessing intraventricular dyssynchrony and other variables of LV function, including EDV, ESV, and EF. A 3-dimensional count distribution was extracted from each of the LV short-axis data sets and subjected to first-harmonic Fourier analysis for systolic dyssynchrony. The Fourier analysis generated a systolic phase distribution ranging from 0° to 360° and spanning the entire R-R interval. The systolic phase distributions for the entire LV were displayed on the polar map and histogram. Two indices were extracted from each phase distribution: histogram bandwidth (HBW), which includes 95% of the elements of the phase distribution, and phase standard deviation (PSD), which is the standard deviation (SD) of the phase distribution. These indices were calculated to assess LV dyssynchrony[12,17].

Statistical Analysis

Descriptive data are expressed as means±SD for continuous variables and as medians and ranges for variables with nonparametric distributions. Categorical variables are expressed as numbers and percentages. The chi-square test or Fisher's exact test was used to compare categorical variables. The Mann-Whitney U-test was used for nonpairwise comparison of nonparametric data between patients with ESRD at baseline and control subjects. Wilcoxon's signed rank test was used for pairwise comparison of nonparametric data between baseline and after 3 months of HD. The relationships of alterations in HBW and PSD between baseline and after 3 months of HD (ΔHBW and ΔPSD) with baseline EDV, LVMI, and systolic blood pressure were analyzed with Spearman's rank correlation. For all analyses, statistical significance was set at $P<0.05$. All statistical analyses were performed with the software package IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

Nineteen subjects were enrolled: 12 patients with ESRD requiring long-term HD and 7 control subjects. The primary causes of ESRD were diabetic nephropathy (n=5), autosomal dominant polycystic kidney disease (n=2), nephrosclerosis (n=2), immunoglobulin A nephropathy (n=1), lupus nephritis (n=1), and gestational kidney disease (n=1). Relevant clinical and demographic characteristics of the subjects are shown in **Table 1**. The bSBP in patients with ESRD (154±15.6 mm Hg) was significantly greater than that in control subjects (122±14.7 mm Hg, $P< 0.0001$). There were no significant differences between ESRD patients and normal controls in age, sex, body-mass index, QRS duration, or diastolic blood pressure. The patients with ESRD were more likely to have comorbid hypertension and to be taking angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists.

Clinical and Biochemical Changes between Baseline and after 3 Months of HD in Patients with ESRD

Between baseline and after 3 months of HD weight increased significantly and systolic blood pressure decreased significantly in patients with ESRD (**Table 2**). Furthermore, levels of hemoglobin, albumin, and blood urea nitrogen increased significantly; hsCRP decreased significantly; but the plasma BNP level showed no significant change.

Table 1 Baseline clinical and demographic characteristics

Variable	Control subjects (n=7)	Patients with ESRD (n=12)	P-value
Age (years)	60±11	60±13	NS
Men	5 (71.4)	7 (58.3)	NS
Body-mass index (kg/m^2)	22.8±1.9	23.9±4.1	NS
QRS duration (ms)	101.0±8.5	101.6±16.7	NS
Heart rate (bpm)	69±6.5	68±11.1	NS
Systolic blood pressure (mm Hg)	122±14.7	154±15.6	<0.0001
Diastolic blood pressure (mm Hg)	74±11.2	79±7.46	NS
Hypertension	0	11 (91.7)	-
Diabetes mellitus	0	5 (41.7)	-
ACEI/ARB	0	10 (83.3)	-
Ca antagonist	0	11 (91.7)	-
Beta-blocker	0	2 (16.7)	-

Data given as mean±standard deviation or n (%).
ESRD, end-stage renal disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin Ⅱ receptor blocker; NS, not significant.

Table 2 Clinical and biochemical alterations from baseline to the third month of hemodialysis

Variable	Baseline	Third month	P-value
Weight (kg)	60.3±13.3	61.1±13.6	<0.05
Systolic blood pressure (mm Hg)	154±15.6	143±9.5	<0.01
Diastolic blood pressure (mm Hg)	79±7.5	76±12.9	NS
Heart rate (bpm)	68±11.1	70±10.6	NS
QRS duration (ms)	101±15.9	98±16.4	NS
Hemoglobin (g/dL)	9.2±1.2	11.4±0.7	<0.001
Albumin (g/dL)	3.3±0.7	3.9±0.6	<0.0001
Urea (mg/dL)	49.4±13.4	59.5±12.0	<0.05
Creatinine (mg/dL)	6.8±2.8	7.9±3.4	NS
Calcium (mEq/L)	8.7±0.7	8.8±0.7	NS
Phosphate (mEq/L)	4.8±1.8	5.4±1.5	NS
Intact parathyroid hormone (pg/mL)	147.5±77.2	116.9±80.6	NS
High-sensitivity C-reactive protein (mg/dL)	1,960±1,859	868±931.7	<0.01
Brain natriuretic peptide (pg/mL)	739.0±982.9	238.4±355.6	NS

Data given as mean±standard deviation; NS, not significant

GSPECT and Echocardiography Data in Control Subjects and Patients with ESRD

At baseline EDV, ESV, and LVMI were significantly greater in patients with ESRD than in control subjects, but the LVEF did not differ significantly between the groups (**Table 3**).

In patients with ESRD, both EDV and ESV decreased significantly between baseline and after 3 months of HD, but EF and LVMI showed no significant change.

LV Dyssynchrony

Examples of improvement in HBW and PSD on phase distribution maps between baseline and 3 months are shown in **Figure 1**. Both HBW and PSD were significantly greater at baseline in patients with ESRD than in control subjects (HBW, 65.5°±54.4° vs. 22.3°±7.5°, P<0.05; PSD, 21.0°±15.5° vs. 7.6°±5.5°, P<0.05) and decreased significantly from baseline to 3 months in patients with ESRD (HBW, 65.5°±54.4° vs. 31.0°±15.7°, P<0.01; PSD, 21.0°±15.5° vs. 10.0°±8.2°, P<0.01) (**Fig. 2**).

Correlations of Changes in HBW and PSD with Baseline EDV, LVMI, and SBP

By Spearman's rank correlation, ΔHBW and ΔPSD were positively correlated with baseline EDV (ΔHBW: r_s= 0.77, P=0.004; ΔPSD: r_s=0.87, P<0.0001; **Fig. 3A, B**) and baseline LVMI (ΔHBW: r_s=0.82, P=0.002; ΔPSD: r_s=0.76, P=0.006; **Fig. 3C, D**) but not with baseline SBP (ΔHBW: r_s=−0.41, P=0.19; ΔPSD: r_s=−0.54, P=0.07).

Discussion

To our knowledge, this study is the first to assess

Table 3 GSPECT and echocardiographic data in control subjects and patients with end-stage renal disease

Variable	Control subjects	ESRD patients		P-value	
		Baseline	3rd month of hemodialysis	Control vs. baseline	Baseline vs. 3rd month
GSPECT					
End-diastolic volume (mL)	72.3±13.9	105.7±29.2	78.6±25.4	<0.05	<0.01
End-systolic volume (mL)	20.9±10.3	44.3±22.1	27.6±16.2	<0.05	<0.01
Ejection fraction (%)	72.1±9.5	60.8±12.6	66.4±12.8	NS	NS
Echocardiography					
LV mass index (g/m²)	65.4±5.6	136.5±48.3	117.2±46.6	P<0.01	NS

GSPECT, gated single-photon emission computed tomography; NS, not significant

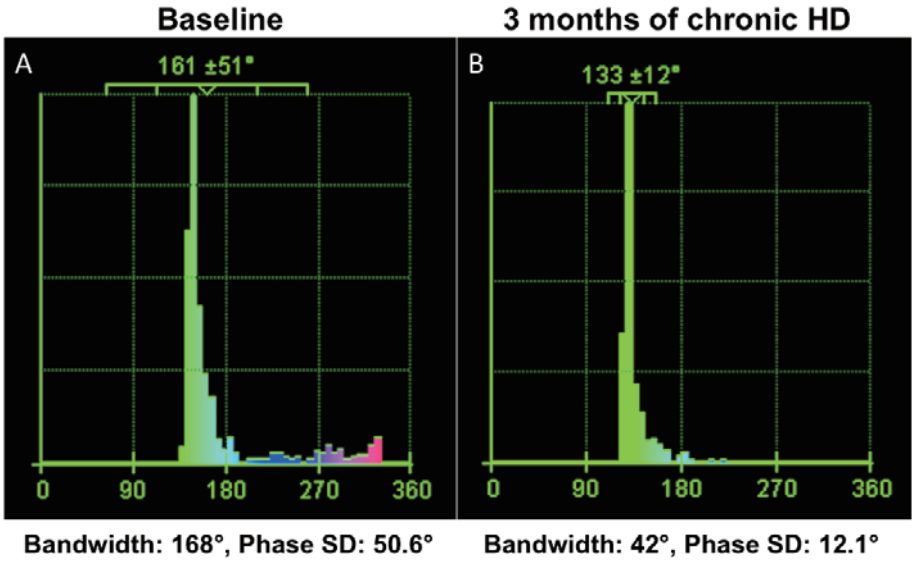

Fig. 1 Improvement in HBW and PSD from baseline (A) to the third month of chronic HD (B) as shown on a phase distribution map. (A) LV dyssynchrony is indicated by the heterogeneous phase angle distribution on the baseline phase histogram. (B) After 3 months of HD, the phase histogram has a narrow bandwidth. HBW, histogram bandwidth; PSD, phase standard deviation; HD, hemodialysis.

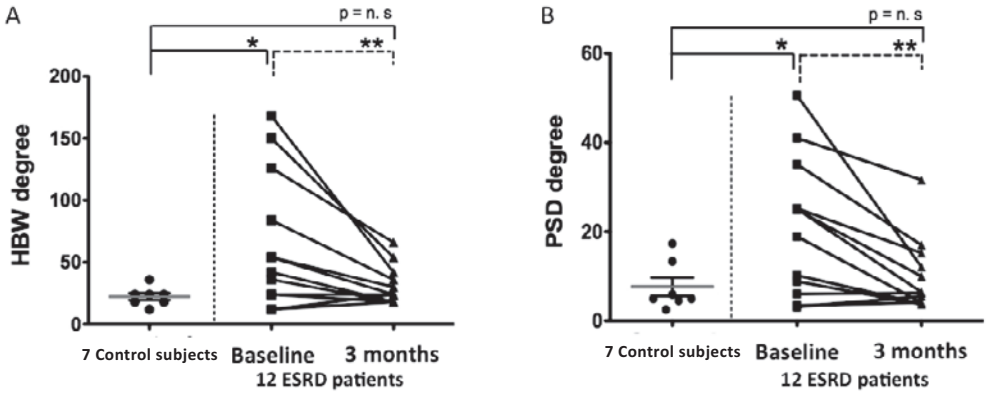

Fig. 2 Plots showing comparisons of LV dyssynchrony in the 7 control subjects (black circle; n=7), the 12 patients with ESRD before the start of long-term HD (baseline, black square; n=12), and the 12 patients with ESRD after 3 months of long-term HD (third month, black triangle; n=12). *P<0.05, control subjects vs. baseline; **P<0.01, baseline vs. third month. LV, left ventricle; ESRD, end-stage renal disease; HBW, histogram bandwidth; PSD, phase standard deviation.

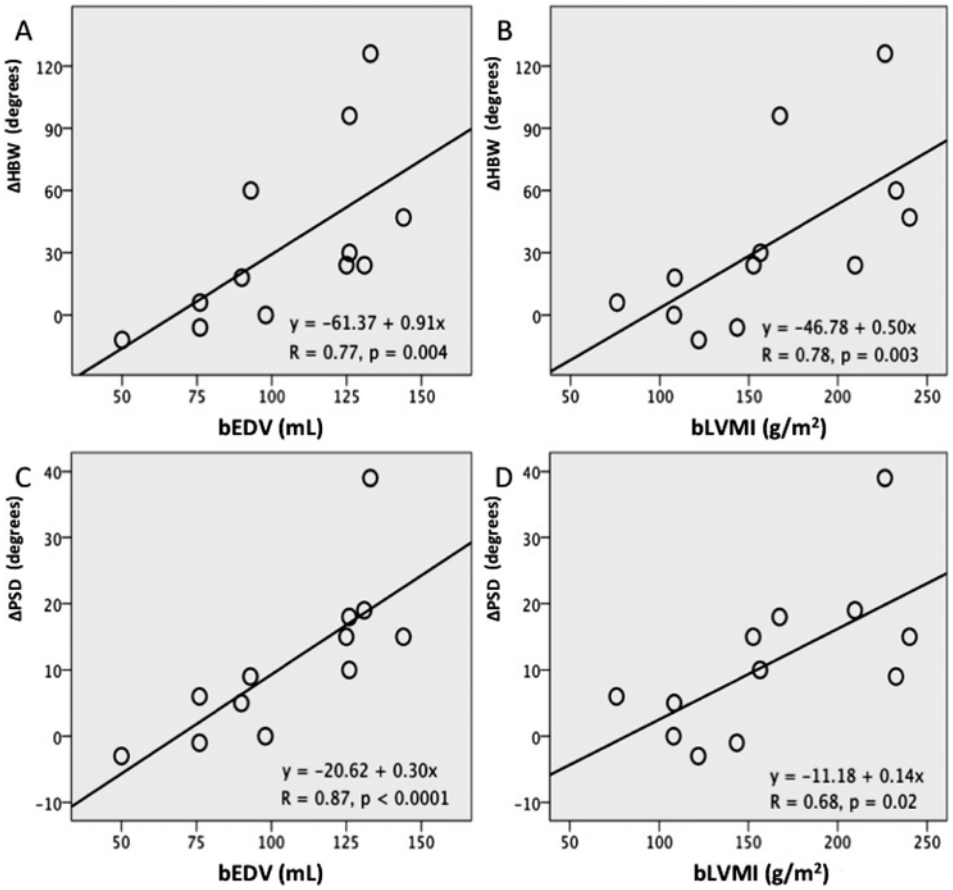

Fig. 3 Representative correlations of ΔHBW (A, C) and PSD (B, D) with bEDV (A, B) and bLVMI (C, D). HBW, histogram bandwidth; PSD, phase standard deviation; bEDV, baseline end-diastolic volume; bLVMI, baseline left ventricular mass index.

changes in LV dyssynchrony, volume, and function from baseline to approximately 3 months after the start of long-term HD (interval, 90–128 days) in patients with ESRD. Our findings indicate that, compared with control subjects, patients with ESRD had significantly greater LV dyssynchrony, volume, and mass at baseline. Phase analysis of GSPECT images demonstrated that long-term HD markedly decreased LV dyssynchrony and volume. In addition, alterations in HBW and PSD correlated well with EDV and LVMI at baseline.

In patients with refractory heart failure and wide QRS, such as those with left bundle-branch block, LV dyssynchrony can contribute to progressive negative remodeling with worsening of pre-existing mitral regurgitation and has been associated with increased mortality rates and adverse cardiovascular outcomes[18]. Recent studies suggest that LV dyssynchrony is also common in patients with narrow QRS and heart failure with preserved EF[19], as well as those with hypertension with LV hypertrophy[20]. In other words, LV dyssynchrony can be caused not only by electrical remodeling, but also by various other factors, such as myocardial tissue damage, LV structural remodeling, and abnormal volume loading[8]. Thus, LV dyssynchrony is likely to be common in patients with ESRD. However, how abnormal volume loading and hypertrophy lead to LV dyssynchrony in these patients remains somewhat unclear. We can speculate that abnormal volume overload and LV structural remodeling resulting in LV hypertrophy are frequent in ESRD patients requiring long-term HD. LV dyssynchrony is exacerbated by excessive volume loading, which intensifies imbalances in the regional stretching and shortening of myocardial fibers[9]. Hayashi et al have demonstrated that high LVMI is independently associated with the presence of LV dyssynchrony in patients with chronic kidney disease[10]. Our results are generally consistent with those of a previous study in which LV mass in patients with ESRD was significantly greater than that in control subjects[9]. Chronic volume and pressure overload combined with metabolic and hormonal impairments may lead to maladaptive LV hypertrophy, which would lead to LV dyssynchrony[21].

In patients with ESRD requiring long-term HD, cardiac abnormalities may result from uremia, fluid retention, or chronic volume overload. Kim et al have reported that the reduction of preload by sublingual nitroglycerin administration decreases LV dyssynchrony[22]. Conversely, preload augmentation by the leg-raising maneuver increases LV dyssynchrony[23]. More recently, 2 studies have examined the acute effects of a single session of HD on LV dyssynchrony and volume in ESRD patients[9,10]. In the present study, we evaluated the effects of long-term HD on LV dyssynchrony by phase analysis of GSPECT images and found that alterations in LV dyssynchrony correlated with baseline LV volume and LVMI. These findings are not fully consistent with those of a study by Hayashi et al[10]. This disagreement might be due to our assessing the long-term, rather than short-term, effects of HD treatment on LV dyssynchrony.

To evaluate the effects of uremic retention solutes on LV dyssynchrony, we measured several biochemical markers, including hemoglobin, albumin, urea, creatinine, calcium, phosphate, intact parathyroid hormone, hsCRP, and BNP. Changes in HBW and PSD were not correlated with changes in biochemical markers. However, serum levels of creatinine were significantly greater after 3 months of HD; this increase might be due in part to long-term HD leading to improved appetite and increased muscle mass. Moreover, 3 months after the start of long-term HD serum levels of hsCRP were significantly decreased, perhaps because of a systemic improvement in uremia.

In many studies of the indications and efficacy of CRT, LV dyssynchrony has been assessed with echocardiography, including tissue synchronization imaging, speckle-tracking strain imaging, and real-time 3-dimensional echocardiography[8,9,24]. Recently, LV dyssynchrony, as assessed with phase analysis of GSPECT images, has been shown to correlate well with indices of intraventricular delay measured with real-time 3-dimensional echocardiography[24] and tissue Doppler imaging, as well as apparently predicting the response to CRT in a preliminary study[25]. The high reproducibility of results obtained by GSPECT with phase analysis makes it comparable in accuracy to any of the echocardiographic techniques currently available[26].

Regarding the assessment of LV dyssynchrony in ESRD, Aljaroudi et al have reported that patients with ESRD have significantly more dyssynchrony than do control subjects[11]. More recently, Aggarwal et al have found that, in patients with ESRD, LV dyssynchrony, as determined by GSPECT with phase analysis, is of greater prognostic value than myocardial perfusion or EF[5]. However, our study is the first GSPECT study of the effects of long-term HD on LV dyssynchrony in patients with ESRD.

Our findings suggest that serial GSPECT with phase analysis is a useful method of assessing the effects of long-term HD on LV dyssynchrony, volume, and function in patients with ESRD.

Limitations

Our study had several limitations. The number of participants was smaller than in similar studies. Because we did not perform stress GSPECT, we were unable to assess the effects of stress-induced ischemia. For each patient with ESRD, GSPECT was performed the day before an HD session, and the issue of radiation exposure prevented us from evaluating the effects of a single session of HD on LV dyssynchrony. Another limitation was that clinical outcomes, including morbidity and mortality, were not examined in detail.

Conclusions

The present study has demonstrated the effects of long-term HD on LV dyssynchrony and volume in patients with ESRD. Changes in LV dyssynchrony correlated positively with bEDV and bLVMI. Serial GSPECT with phase analysis is a useful method for assessing the effects of long-term HD on LV dyssynchrony, volume, and function in patients with ESRD.

Acknowledgments: The authors thank Mr. Hiroshi Akimoto, Mr. Shigeki Ikeda, Mr. Teruo Takahashi, and Mr. Osamu Imuta for their work on image acquisition and processing.

Conflict of Interest: The authors have no conflicts of interest to declare.

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(Received, October 27, 2014)
(Accepted, December 8, 2014)