Elevated E/E' Predicts Cardiovascular Events in Hemodialysis Patients with Preserved Systolic Function

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Abstract

Objective We conducted a cohort study to investigate whether diastolic function could predict cardiovascular (CV) events in 161 HD patients with preserved systolic function.

Materials and Methods The ratio of early transmitral flow velocity to early mitral annular velocity (E/E') was measured by tissue Doppler imaging. Patients were stratified into two groups based on whether they experienced a CV event.

Results During a 4-year follow-up period, 64 patients experienced a CV event. The E/E' values (15.18 ± 5.78) in the CV-event group were significantly higher than in the group who had not experienced a CV event (12.32 ± 4.23). Kaplan-Meier analysis indicated that the incidence of CV events was significantly higher in the group of patients whose E/E' was >15 than in the group whose E/E' was ≤ 15 (log-rank $p=0.0016$). Multivariate Cox proportional hazards regression analysis revealed the E/E' ratio to be a significant predictor of CV events in HD patients with preserved LV systolic function.

Conclusion The results of this study showed that elevated E/E' ratio in chronic HD patients predicts CV events better than other echocardiographic parameters.

Key words: diastolic dysfunction, echocardiography, cardiovascular event, hemodialysis

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Introduction

The high mortality of hemodialysis (HD) patients is mainly attributable to cardiovascular (CV) disorders, which are responsible for more than 40% of the deaths in this patient group (1, 2). Although the higher risk of CV disorders in HD patients is likely due to their severely compromised CV state, HD patients without any apparent CV disorder are also at higher risk of future CV events. Thus, identifying HD patients with an increased CV risk is of clinical importance and would enable preventive measures to be implemented.

The incidence of heart failure despite preserved left ventricular (LV) systolic function has recently increased and now comprises nearly 50% of congestive heart failure patients (3). Although LV filling alterations are often detected in HD patients, the actual prevalence of diastolic dysfunction

and its impact on the clinical course are not fully understood (4). It is therefore important to detect the presence of advanced diastolic dysfunction, which is characterized by an increase in the filling pressure, especially in the subclinical phase. The ratio of early transmitral flow velocity to early mitral annular velocity (E/E') measured by the tissue Doppler imaging (TDI) technique has recently been proposed as an index of LV filling pressure (5, 6).

The purpose of this study was to investigate whether an elevated E/E' ratio, as an index of LV diastolic function, predicts CV events in chronic HD patients.

Materials and Methods

Study population

This was a prospective, single-center cohort study and was conducted over a 4-year follow-up period. A total of

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190 HD patients were recruited from among patients who had been routinely treated in the dialysis unit of the Hidaka Hospital for at least 6 months and were receiving standardized HD prescriptions (500 mL/min dialysate flow; 200-250 mL/min blood flow; 4 hours of dialysis per session; 3 sessions per week). The exclusion criteria were: a malignancy, active infection, nonsinus rhythm, pericardial effusion, and evidence of major valvular heart disease. Sixteen subjects were excluded based on the exclusion criteria. The Institutional Research Ethics Committee approved the study protocol, and the study was conducted in compliance with the Declaration of Helsinki.

Of the 174 HD patients who were eligible to participate, 166 (age: 61.0 ± 12.0 years, dialysis vintage: 9.0 ± 8.0 , male/female=107/59) gave their informed consent and underwent echocardiography between January 2005 and December 2006. Of the 166 patients recruited, five patients were excluded because of incomplete data collection, and the 161 remaining patients (mean age: 61.2 years, mean dialysis vintage: 9.2 years, male/female=102/59) were assessed as subjects of this study. The underlying disease was chronic glomerulonephritis in 91 patients, diabetic nephropathy in 45 patients, nephrosclerosis in 11 patients, polycystic kidney disease in 9 patients, chronic pyelonephritis in 3 patients, and lupus nephritis in 2 patients. The subjects' demographic and clinical data, including age, gender, and systolic and diastolic blood pressure (BP), were recorded at entry. BP was measured three times after the subject had rested in the supine position for at least 10 min, and the average of the three measurements was adopted. Pulse pressure was calculated by subtracting diastolic BP from systolic BP. Body surface area (BSA) was calculated according to a simplified formula: $0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$.

Laboratory tests

Blood was drawn in a fasting state immediately before starting a dialysis session. The serum creatinine, albumin, calcium, phosphate, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, blood glucose, and C-reactive protein (CRP) levels and the hemoglobin concentration were measured by routine laboratory methods. The mean values of 3 measurements made during each of the 3 months before echocardiography were used in the analysis. Serum intact parathyroid hormone (PTH) was measured once when echocardiography was performed. Information on treatment with intravenous erythropoiesis-stimulating agents (ESAs) and prescription of anti-hypertensive agents, vitamin D, and lipid-lowering drugs was collected from the medical records.

Echocardiography

An experienced senior cardiosonographer performed the echocardiographic studies with an Aplio XV (Toshiba, Tokyo, Japan) ultrasound imager equipped with a 2.2/4.4 MHz (harmonics) phased-array 3S transducer during continuous electrocardiographic recording, as previously described (7).

The data were saved in the device's archive (digital archive, raw data), and the images obtained were recalled for calculation of the study parameters by the same interpreter, who was unaware of the patients' clinical status. To minimize the effect of fluid overload, the echocardiographic evaluation was performed after a dialysis session. The two-dimensional guided M-mode echocardiographic study of the LV was performed in the parasternal long-axis view, and LV end-systolic diameter (LVDs), LV end-diastolic diameter (LVDd), interventricular septum thickness (IVST), and posterior wall thickness (PWT) were recorded as the mean values measured in five consecutive cardiac cycles, in accordance with the recommendations of the American Society of Echocardiography (8). LV systolic function was determined based on the ejection fraction (EF) calculated by using a modified biplane Simpson's method from apical two- and four-chamber views (9), and systolic dysfunction was defined as an EF <50%. LV mass was calculated by the method described by Devereux et al (10). LV mass index (LVMI) was calculated by dividing LV mass by BSA, and LV hypertrophy was defined as an LVMI >131 g/m² for men and >100 g/m² for women (11). LA diameter (LAD) was measured in the parasternal long-axis view by making a leading edge-to-leading edge measurement of the maximal distance between the end-systolic posterior aortic root wall and posterior LA wall in accordance with the American Society of Echocardiography guidelines (12). This method has been shown to minimize inter-observer and intra-observer error (13). At the same time, measurements of cardiothoracic ratio (CTR) were performed for estimating dry weight.

TDI measurement

The tissue Doppler program was set in the pulsed-wave Doppler mode as previously described (7). Motion of the mitral annulus was recorded in the apical four-chamber view. Sample volumes were positioned sequentially at the lateral and septal corners of the mitral annulus. A pulsed-wave Doppler examination of mitral inflow and Doppler tissue imaging of the lateral mitral annulus were performed in each subject (14). In an attempt to provide a continuous variable, the ratio of the mitral inflow early diastolic filling velocity (E) to the mitral annular early diastolic velocity (E') was used as an approximation of mean left atrial pressure (E/E') (15). E' was used as a measure of the speed of LV relaxation, because E' has been shown to correlate inversely with the time constant of isovolumic relaxation and is considered relatively preload-independent. All measurements were made by the same examiner under blind conditions.

Follow-up study

After the initial assessment, patients were followed up by the nephrologists who participated in the study for 4 years. During the follow-up period, CV events (electrocardiogram-documented angina episodes and myocardial infarction, heart failure, electrocardiogram documented arrhythmia,

Table 1. Comparison of Demographic and Clinical Characteristics of Hemodialysis Patients with and without Cardiovascular Events

	Event-free (n = 97)	Event (n = 64)	p value
Age (years)	59.0 ± 12.4	64.6 ± 10.6	0.0038
Gender (men)	59 (60.8%)	43 (67.2%)	0.4122
Dialysis vintage (months)	114.3 ± 93.7	106.3 ± 100.3	0.6081
Diabetes (n, %)	21 (21.7%)	24 (37.5%)	0.0283
Body mass index (kg/m ²)	21.1 ± 3.8	21.7 ± 3.7	0.3733
Systolic blood pressure (mmHg)	132.7 ± 21.4	140.3 ± 27.5	0.0516
Diastolic blood pressure (mmHg)	77.6 ± 11.3	77.8 ± 13.4	0.8964
Pulse pressure (mmHg)	55.2 ± 14.5	62.5 ± 18.9	0.0064
Cardiothoracic ratio (%)	48.8 ± 5.3	48.3 ± 4.1	0.5147
Creatinine (mg/dL)	11.5 ± 2.9	10.6 ± 3.2	0.0586
C-reactive protein (mg/dL)	0.3 ± 0.8	0.4 ± 0.7	0.6616
Albumin (g/dL)	3.8 ± 0.3	3.7 ± 0.3	0.0382
Total cholesterol (mg/dL)	148.6 ± 31.9	152.1 ± 35.8	0.5226
HDL cholesterol (mg/dL)	44.2 ± 12.7	41.6 ± 10.6	0.1814
Triglyceride (mg/dL)	107.9 ± 61.9	109.7 ± 70.1	0.8630
Calcium (mg/dL)	8.9 ± 0.9	8.7 ± 0.9	0.2745
Phosphorus (mg/dL)	6.2 ± 1.2	5.9 ± 1.1	0.0954
Intact PTH (pg/mL)	228.4 ± 129.4	205.4 ± 123.5	0.2621
Hemoglobin (g/dL)	10.2 ± 1.1	10.2 ± 0.9	0.8566
ESA (n, %)	24 (24.7%)	20 (31.3%)	0.3645
Vitamin D (n, %)	56 (57.3%)	29 (45.3%)	0.1224
Anti-hypertensive agents (n, %)	61 (62.9%)	47 (73.4%)	0.1633
Lipid-lower agents (n, %)	16 (16.5%)	17 (26.6%)	0.1215

HDL, low-density lipoprotein; PTH, parathyroid hormone; ESA, erythropoiesis-stimulating agents.

transient ischemic attack, stroke, and other thrombotic events except arteriovenous fistula thromboses) were accurately recorded. Each event was reviewed and assigned an underlying cause by two physicians. As a part of the review process, all available medical information about each CV event was collected. This information included study and hospitalization records.

Statistical analysis

All statistical analyses were performed using the JMP 9.0 software program (SAS Institute, Cary, NC, USA). Continuous data were expressed as means ± SD, and categorical data were expressed as a number (percentage). Comparisons between the two groups were made by the *t*-test or chi-squared test. The relationship between paired variables was analyzed by calculating the Pearson sample correlation coefficient. Survival was estimated on the basis of the Kaplan-Meier curves, and compared using the log-rank test. The independent prognostic value of E/E' for all-cause mortality was analyzed by multiple Cox regression analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by using the estimated regression coefficients and standard errors in the Cox regression analysis. *p* values <0.05 were considered statistically significant.

Results

One hundred sixty-one subjects were assessed. During the

follow-up period of 4 years, 64 patients (39.8%) experienced CV events, including acute myocardial infarction, symptomatic angina, heart failure, stroke, and peripheral artery disease. Table 1 compares the demographic and clinical parameters of the group of patients who experienced a CV event (CV-event group) and the group that did not (non-CV-event group). The CV-event group was significantly older, had a higher rate of diabetes, and had higher pulse pressure and lower serum albumin levels than the non-CV-event group. There were no significant differences in gender, dialysis vintage, systolic or diastolic BP, CTR, hemoglobin concentration, serum lipid, calcium, phosphate, or intact PTH levels, or the use of anti-hypertensive agents, lipid-lowering drugs, vitamin D, or ESAs between the two groups (Table 1).

Table 2 compares the echocardiographic parameters of the groups of patients according to whether they had experienced a CV event. The E/E' values in the CV-event group (15.18 ± 5.78) were significantly higher than in the non-CV-event group (12.32 ± 4.23). There were no significant differences between the groups in other echocardiographic parameters, including LV systolic function (EF and FS), LV diastolic function (E/A ratio and DCT), or LV geometry (IVST, PWT, LVMI, LVDd, and LVDs). However, there was a positive correlation between the E/E' values and LVMI values (*r*=0.187, *p*=0.0173) and E/A ratios (*r*=0.325, *p*<0.0001) in the group of subjects as a whole.

Kaplan-Meier analysis indicated that the incidence of CV

Table 2. Comparison of Echocardiographic Parameters of Hemodialysis Patients with and without Cardiovascular Events

	Event-free (n = 97)	Event (n = 64)	p value
EF (%)	67.78 ± 7.42	65.67 ± 7.51	0.0809
LAD (cm)	3.98 ± 0.59	4.12 ± 0.64	0.1497
IVST (mm)	10.18 ± 2.15	10.30 ± 2.12	0.7366
PWT (mm)	10.38 ± 1.87	10.48 ± 1.36	0.7166
LVMI (g/m ²)	118.88 ± 39.45	124.41 ± 56.78	0.4671
LVDd (cm)	4.95 ± 0.59	4.91 ± 0.69	0.6901
LVDs (cm)	3.06 ± 0.49	3.13 ± 0.56	0.4559
FS (%)	38.22 ± 5.90	36.52 ± 5.86	0.0761
DCT (ms)	237.75 ± 77.84	255.80 ± 64.85	0.1266
E/E' ratio	12.32 ± 4.23	15.18 ± 5.78	0.0004

EF, ejection fraction; LAD, left atrial diameter; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVMI, left ventricular mass index; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; FS, fractional shortening; E/A, ratio of early transmitral flow velocity to late transmitral flow velocity; DCT, deceleration time of the early transmitral flow velocity; E/E', ratio of early transmitral flow velocity to early mitral annular velocity.

Figure 1. Kaplan-Meier survival plot of the cardiovascular event-free survival rate during follow-up of 161 hemodialysis patients in a group whose E/E' ratio was ≤15 and in a group whose E/E' ratio was >15.

events was significantly higher in the group of patients whose E/E' ratio was >15 than in the group of patients whose E/E' ratio was ≤15 (log-rank $p=0.0016$; Fig. 1). Multivariate Cox proportional hazards regression analysis revealed that the E/E' ratio was a significant predictor of CV events in HD patients with preserved LV systolic function (Table 3).

Discussion

The results of the present study showed that an elevated E/E' ratio was an independent risk factor for CV events during a 4-year follow-up period of chronic HD patients whose EF was >50%. During the 4-year follow-up period, 64 patients (39.8%) experienced a CV event, confirming that the HD patients had a high risk of CV events even though their LV systolic function was preserved. The incidence of CV events was lower in the group of patients without LV diastolic dysfunction. Moreover, Kaplan-Meier analysis indicated that there was a higher cumulative incidence rate of

CV events in the group of patients with LV diastolic dysfunction than in the group without diastolic dysfunction. These results clearly showed that LV diastolic dysfunction at baseline is an important determinant of the future incidence of CV events in chronic HD patients.

Abnormal LV size and function are encountered in 70-80% of incident dialysis patients (16). These alterations develop early in the course of renal disease, and their prevalence increases in parallel with the decline in renal function (17). The process of LV dilatation and compensatory hypertrophy continues after the start of dialysis therapy, especially in the first year (18). Foley et al (19) found that clinical signs of cardiac dysfunction were more frequent in a cohort study of 433 patients on dialysis, and echocardiography revealed an even greater prevalence of abnormalities: systolic dysfunction in 15%, LV dilatation in 32%, and LV hypertrophy in 17%. An increase in LV cavity volume was associated with CV mortality when there is LV cavity dilatation. Thus, LV diastolic dysfunction seems to be an early sign of LV remodeling in HD patients.

Clinically evident heart failure at the start of HD therapy is an independent predictor of mortality in starting HD therapy (19), and identification of the underlying cause can be important to directing the therapeutic management of HD patients with CV disorders. Detecting LV diastolic dysfunction and estimating LV filling pressure are currently of general interest to predict the risk of developing heart failure in HD patients with preserved LV systolic function. According to the recent definition and consensus statement of the European Society of Cardiology, the diagnosis of diastolic heart failure is based on clinical symptoms and parameters measured by echocardiography (20) and the E/E' ratio has been identified as one of the tools that is useful for assessing diastolic dysfunction and LV filling pressure. In addition, the E/E' ratio calculated by the TDI technique has recently been proposed as an index of LV filling pressure in the general

Table 3. Multivariate Cox Proportional Hazards Regression Analysis Demonstrating the Relation between Cardiovascular Events and Variables Obtained at Baseline

	HR	95%CI	p value
E/E' ratio	1.070	1.019-1.118	0.0078
EF (/1%)	0.950	0.918-0.982	0.0029
Age (/1year)	1.025	0.998-1.056	0.0728
DM (vs. Non-DM)	1.254	0.667-2.311	0.0733
Pulse pressure (/1mmHg)	1.007	0.988-1.028	0.4790
Albumin (/1g/dL)	0.411	0.147-1.150	0.4764
Cardiothoracic ratio (/1%)	0.946	0.887-1.005	0.0904

population (5, 6).

However, the diagnosis of diastolic dysfunction should be refined, but stratifying the CV risk in HD patients has been little investigated. Sharma et al (21) found an association between E/E' ratios >15 and higher all-cause mortality in a study of 125 candidates for kidney transplantation. However, only one-third of the patients were on HD, and only a univariate analysis was performed, which did not allow assessment of whether the E/E' ratio adds prognostic value to the traditional assessment of CV risk in this group. Based on their findings in a study of 220 patients on peritoneal dialysis, Wang et al (22) reported that E/E' ratios >15 predicted all-cause and CV mortality better than the classic clinical and echocardiographic data.

Mimura et al (23) found that LV dilatation was significantly more frequent in a CV cause of death group than in a non-CV cause of death group, and that the cross-sectional area of the LV was significantly larger in the CV cause of death group. These findings indicated a more severely dilated LV in the CV cause of death group. The mechanism and progression of the LV dilatation are not completely understood. Many factors affect LV function and transmitral flow: preload, afterload, heart rate, LV mass, metabolic and humoral parameters, myocardial innervation, and microangiopathic lesions (24). LV diastolic dysfunction is the result of a combination of abnormal relaxation and compliance. Compliance abnormalities occur at a later stage. When compliance is poor, a slight increase in preload can induce a sharp increase in LV pressure and lead to congestion and pulmonary edema. A small decrease in filling pressure, on the other hand, can reduce systolic ejection volume and cardiac output.

Kimura et al (25) recently reported that LVMI is an independent determinant of LV diastolic dysfunction in HD patients with preserved LV function. The late stage of LV hypertrophy leads to both diastolic and systolic dysfunction and ultimately to clinically recognizable congestive heart failure, which has a definite adverse effect on the long-term survival of HD patients (26). The E/E' ratio was positively correlated with LVMI in the subjects of our study, but LVMI did not predict adverse outcomes. Such discrepant findings can partly be explained by the different study popu-

lations. Another reason for the discrepancy seems to be that in our study echocardiography was performed after a HD session, since it has been reported that TDI parameters and LVMI measurements should be made in a relatively normovolemic state, typically on the day after HD (27).

Study had several limitations. First, there was an inherent limitation in the observational study design. Second, we were not able to assess extracellular fluid volume/total body water ratio measured by multifrequency electric bioimpedance. However, this assessment tool has not yet been validated in HD patients. Third, echocardiographic parameters might act as confounding factors to other parameters, because the values of most of the parameters were correlated with each other. Nevertheless, the E/E' ratio was the strongest predictor for CV events in HD patients with preserved LV systolic function in a multivariable Cox model, even after adjustment of such parameters. Finally, the echocardiographic examinations were performed only at the start of this study. Whether the echocardiographic findings remained unchanged during the follow-up period is unknown. Serial follow-up echocardiography examinations may be helpful in understanding the natural history of LV diastolic dysfunction in HD patients. Whether a decrease in the E/E' ratio translates into a lower risk of CV events requires further study.

In conclusion, the results of the present study showed that an elevated E/E' ratio predicts CV events better than other echocardiographic parameters in chronic HD patients with preserved LV systolic function. They also suggest that measurement of the E/E' ratio may be helpful in risk stratification and in providing therapeutic direction for the management of HD patients.

The authors state that they have no Conflict of Interest (COI).

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