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Evaluation of echocardiographic indices for the prediction of major adverse events during long-term follow-up in chronic hemodialysis patients with normal left ventricular ejection fraction

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Abstract. – *Background:* Cardiovascular disease is the leading cause of mortality in end-stage renal failure. Prognostic role of echocardiography has not been fully elucidated in chronic hemodialysis patients.

Aim: To assess the ability of Doppler echocardiographic parameters of left ventricular (LV) diastolic function along with conventional echocardiographic indices to predict long-term adverse major events in chronic hemodialysis patients with normal LV ejection fraction (EF).

Patients and Methods: A total of 45 chronic hemodialysis patients (aged 49 ± 15 years) were included to the study. All patients underwent complete standard and tissue Doppler imaging echocardiography before and immediately after hemodialysis session and were followed-up prospectively. Major outcome measure was the combination of all-cause death and hospitalization for any cardiovascular event.

Results: During the follow up period (52 ± 26 months) 23 major events occured (17 all-cause deaths and 6 cardiovascular events requring hospitalization). Post-dialytic values of mean left atrial diameter, mitral E (peak early mitral inflow velocity), E/Vp [ratio of mitral E to flow propagation velocity (Vp)] and E/Ea [ratio of mitral E to peak early diastolic mitral annular velocity (Ea)] (average of 4 segments of mitral annulus) were significantly higher in patients who had major events. In Cox proportional hazard analysis only E/Ea ratio predicted combined endpoint of all-cause mortality and nonfatal cardiovascular events (hazard ratio: 1.20; confidence interval: 1.03-1.39; p =0.018). The optimum cut-off value for E/Ea determined by ROC curve analysis revealed that E/Ea ratio higher than 9.8 predicted future events with sensitivity of 74% and specificity of 86%.

Conclusions: E/Ea might be an accurate echocardiographic indice during long-term follow up for the prediction of major adverse events in chronic hemodialysis patients with normal LV EF.

Key Words:

Adverse events, Cardiovascular outcomes, Doppler, Echocardiography, Hemodialysis.

Introduction

Cardiovascular complications are the leading cause of mortality among patients on chronic hemodialysis, accounting for about 50% of all deaths[1-3]. Numerous reports indicate that, in contrast to general population, conventional atherosclerotic risk factors such as hypertension, hyperlipidemia and obesity do not entirely explain the observed cardiovascular mortality in hemodialysis patients[4]. Besides, low blood pressure, low total cholesterol and low body mass index (BMI) are shown to be associated with a higher risk of adverse cardiovascular outcomes[5-7]. Existence of this reverse epidemiology indicate potential discrepancies regarding underlying pathophysiologic mechanisms in this particular patient population. Myocardial involvement is one of the proposed mechanisms[8,9]. Hence, echocardiographic evaluation might play a pivotal role in establishing myocardial dysfunction and determining the cardiovascular risk. In this regard, the association between left ventricular (LV) systolic dysfunction and mortality has been well-defined in hemodialysis patients[10]. However, only few studies have evaluated the utility of diastolic parameters for predicting cardiovascular events. The aim of this study was to assess the ability of Doppler echocardiographic parameters of LV diastolic

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function along with conventional echocardiographic indices to predict long-term adverse major events in stable chronic hemodialysis patients with normal LV ejection fraction (EF).

Patients and Methods

Study Patients

This study was conducted in Cardiology and Nephrology Departments of Selcuk University, Meram School of Medicine with the approval of the Institutional Ethics Committee and all patients provided written informed consent. Among the patients referred to the Nephrology Department of Selcuk University Hospital for hemodialysis, 45 subjects were selected randomly and prospectively included in the study. All of the patients were on maintenance hemodialysis -three days a week- for at least 6 months. Patients with significant valvulopathy (any degree of mitral or aortic stenosis and moderate to significant mitral, aortic or tricuspit regurgitation, mitral valvuloplasty or mitral valve operation), LV ejection fraction ≤50%, segmental wall motion abnormaly, pericardial effusion, uncontrolled hypertension, known coronary artery disease or suspicion of clinically coronary artery disease were excluded from the study. Other exclusion criteria were any symptom or sign indicating decreased functional capacity, volume overload or heart failure, having rhythm other than sinus or bundle branch block, history of cerebrovascular event, transient ischemic attack or peripheral vascular disease and anemia with hemoglobin levels below 10 g/dl.

Echocardiographic Examination

Two-dimensional echocardiographic and Doppler measurements were performed 1 hour before and immediately after a routine hemodialysis session, using an ATL 5000 (Advanced Technology Laboratories, Bothell, WA, USA) echocardiography device equipped with variable frequency phased-array transducer (2-4 MHz with harmonic imaging feature). The images were obtained with the patient in the left lateral decubitus position during quiet expiration.

M-mode echocardiography was performed to evaluate LV end-diastolic diameter, LV end-systolic diameter, interventricular septum thickness, posterior wall thickness and left atrial diameter, according to the American Society of Echocardiography recommendations[11]. LV mass was calculated according to Deveraux Formula and was divided by estimated body surface area to determine LV mass index[11,12].

The pulsed Doppler transmitral flow velocity profile [peak velocity of early filling (E), peak velocity of atrial filling (A), the E/A ratio, E deceleration time (EDT)] was obtained from the apical four-chamber view with the sample volume positioned between the mitral leaflet tips. Pulmonary venous flow was obtained with the sample volume placed 1 cm beyond the orifice of the right superior pulmonary vein from the apical four-chamber view. Pulmonary venous peak flow velocities of systolic (PV_s), diastolic (PV_d) and atrial reversal (PV_r) waves were recorded.

Tissue Doppler imaging (TDI) was performed in the 4- and 2-chamber apical views, with the ultrasound beam perpendicular to the mitral annular plane. A 3.5 mm sample volume was placed at the septal, lateral, anterior and inferior aspects of the mitral annulus. Peak early diastolic (E_a), peak late diastolic (A_a) and peak systolic (S_a) velocities were measured. In the TDI images, the systolic velocity duration was measured as ejection time (ET). The time between the end of the systolic velocity and the beginning of early diastolic velocity was recorded as isovolumic relaxation time (IRT), whereas the time between the end of the late diastolic velocity and the beginning of systolic velocity was recorded as isovolumic contraction time (ICT). All values obtained from 4 different sites (septal, lateral, anterior and inferior) of the mitral annulus were averaged to calculate mean values. Average values of TDI measurements were used to avoid possible effects of subtle regional dysfunction which has been well-established in left ventricular hypertrophy and hypertension[13,14].

Measurement of flow propagation velocity (V_p) from color M-mode Doppler, as described by Garcia et al[15], was determined by the slope of the first clearly demarcated isovelocity line during early filling, from the mitral valve plane into the LV cavity. E/E_a and E/V_p ratios were calculated as predictors of LV filling pressure[15-17].

Myocardial performance index (MPI) is defined as the sum of ICT and IRT divided by ET[18]. TDI-derived MPI was calculated using the parameters obtained by TDI in the equation (ICT+IRT)/ET. The values obtained from 4 different sites of the mitral annulus were averaged to calculate mean TDI-derived MPI.

All tracings were recorded at a sweep speed of 100 mm/s and three continuous beats were obtained and averaged for the analysis.

Analysis of Survival

Participants were followed from December 2003 until October 2011 or time of death or transplantation. Major outcome measure evaluated was, combination of all-cause death and hospitalization for a cardiovascular event during the follow-up period. Cardiovascular events were defined as acute myocardial infarction, hospitalization for unstable angina or acute heart failure, coronary or peripheral artery revascularization (by percutaneous intervention or bypass surgery), ischemic or hemorrhagic stroke. Outcomes were obtained by review of inpatient and outpatient medical reports. In case of death out of hospital, circumstances surrounding death were ascertained by telephone contact with family members or attending physician of the dialysis center. Patients who underwent kidney transplantation were censored. For patients who had multiple events, data were censored at the time of the first event. No patient was lost to follow up.

In their study evaluating preload dependency of Doppler techniques, Ie et al[19] demonstrated that assessment of diastolic function shortly before hemodialysis have the potential to underestimate the degree of diastolic dysfunction. Therefore, post-dialytic echocardiographic measurements were used in statistical and survival analysis. Echocardiographic indices of diastolic dysfunction have been previously validated with invasive measurements in many trials[15-17]. Hence, cardiac catheterization was not performed as the study population consisted of the patients without any clinical evidence of cardiovascular disease.

Statistical Analysis

All data were expressed as mean ± standard deviation or percentages as appropriate. Mann–Whitney U and 2-tailed Student's t-tests were used for analysis of numerical variables. Comparisons of categorical data were performed by Pearson's chi-square test. Cox proportional hazard model was used to evaluate the independent factors that influenced the combined endpoint of all-cause mortality and hospitalization for a cardiovascular event. Minimal sample size required for the regression analysis to achieve a statistical power of 80% with a type I error <0.10 and with an anticipated effect size of 0.35 was 43. Covariates entered into the model were echocardiographic parameters those were reported to be associated with mortality in previous studies evaluating chronic hemodialysis patients (LV ejection fraction, LV mass index, LA diameter)[10,20,21]. Moreover, adjustment for age, gender and hemodialysis duration was performed during the analysis. Mitral E was not included in survival analysis because of its direct correlation with E/V_p and average E/E_a. Receiver operating characteristic (ROC) curves were generated to identify the optimal cut-off values of indices to predict the combined endpoint. The validity of the model was measured by means of the area under ROC curve and positive and negative likelihood ratios (+LR and –LR). Kaplan-Meier survival analysis was performed to examine the difference in combined endpoint between the two groups according to the cut-off values determined by the ROC curves. The log-rank test was used to evaluate the differences between Kaplan-Meier curves. A p value less than 0.05 was considered to be statistically significant. Data were analyzed by using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 45 chronic hemodialysis patients aged from 16 to 74 years old (49 ± 15 years) were included to the study. During the follow up period (52 ± 26 months, median: 43 months) 17 patients died due to any cause, 6 patients were hospitalized due to cardiovascular conditions and 6 patients underwent renal transplantation. The cause of the adverse outcomes are summarized in Table I.

Comparison Between Patients With and Without Events

Mean left atrial diameter, mitral E, E/V_p, average E_a and E/E_a were significantly higher in patients who had major events compared to those without, though there was no significant difference in age, sex, duration of hemodialysis, prevalence of hypertension, diabetes mellitus and smoking. Mean values of echocardiographically measured LV ejection fraction, LV mass index, mitral A, E/A ratio, EDT, PV_s, PV_d, PV_r, Vp did not differ significantly between the groups (Table II). Moreover, peak systolic myocardial velocities and TDI-derived MPI which were obtained from the septal, lateral, anterior and inferior aspects of the mitral annulus and their averages (Table II) did not differ significantly between the groups.

Table I. Causes of all-cause mortality and hospitalization for a cardiovascular event during the follow-up period.

	Number of patients
All-cause deaths	
ST-elevation myocardial infarction	5
Non- ST elevation myocardial infarction	1
Acute heart failure	3
Sudden cardiac death	3
Septic shock	2
Acute pulmonary embolism	1
Postoperative ventricular fibrillation	1
Hemorrhagic stroke	1
Hospitalization for cardiovascular events	
Acute heart failure	2
Percutaneous coronary intervention	2
Coronary artery bypass surgery	1
Femoropopliteal bypass surgery	1

Predictors of Events

In Cox proportional hazard analysis, only average E/E_a ratio predicted combined endpoint of all-cause mortality and nonfatal cardiovascular events requring hospitalization [hazard ratio: 1.20; 95% confidence interval (CI): 1.03-1.39; $p = 0.018$)] (Table III). The optimum cut-off value for E/E_a determined by ROC curve was 9.8. E/E_a ratio higher than 9.8 predicted future events with sensitivity of 74% and specificity of 86%. The area under curve was 0.86 (95% CI: 0.75-0.97; $p < 0.001$) (Figure 1). The positive likelihood ratio was 5.42 whereas the negative likelihood ratio was 0.30. On Kaplan–Meier survival analysis, patients with E/E_a ratio higher than 9.8 exhibited a significantly worse event free-survival than those with E/E_a ratio lower than 9.8 (15% vs. 76%, log-rank: 9.81, $p = 0.002$) (Figure 2).

Table II. Demographic, clinical and echocardiographic variables of the study population.

Variable	Total (n = 45)	Patients with events (n = 23)	Patients without events (n = 22)	*p* value
Age(years)	49 ± 15	51 ± 15	47 ± 15	0.37
Women	23 (51.1)	12 (52.2)	11 (50.0)	0.88
HT	28 (62.2)	15 (65.2)	13 (59.1)	0.67
DM	15 (33.3)	8 (34.8)	7 (31.8)	0.83
Smoking	10 (22.2)	5 (21.7)	5 (22.7)	0.94
Duration of HD (months)	51 ± 31	51 ± 34	51 ± 28	0.99
LA (mm)	36 ± 7	38 ± 6	33 ± 7	0.04
LVEDd (mm)	45 ± 7	46 ± 8	45 ± 7	0.59
LVESd (mm)	28 ± 6	29 ± 8	27 ± 5	0.32
LV EF	68 ± 8	67 ± 9	70 ± 6	0.13
LV mass	193 ± 65	199 ± 72	188 ± 59	0.57
LV mass Index	116 ± 37	120 ± 39	112 ± 35	0.50
E (cm/s)	67 ± 22	75 ± 26	59 ± 15	0.02
A (cm/s)	72 ± 21	76 ± 27	68 ± 13	0.20
E/A ratio	0.97 ± 0.55	1.04 ± 0.71	0.90 ± 0.29	0.38
EDT (cm/s)	185 ± 24	183 ± 27	187 ± 20	0.60
PVs (cm/s)	48 ± 13	48 ± 14	49 ± 13	0.86
PVd (cm/s)	41 ± 12	42 ± 14	40 ± 9	0.55
PVr (cm/s)	26 ± 5	25 ± 5	27 ± 5	0.34
Vp	62 ± 24	56 ± 19	67 ± 28	0.13
E/Vp	1.28 ± 0.69	1.49 ± 0.77	1.06 ± 0.54	0.03
Ea†	7.7 ± 3.4	6.4 ± 2.6	9.1 ± 3.5	0.004
E/Ea†	9.57 ± 3.93	11.97 ± 3.63	7.06 ± 2.39	< 0.001
Aa†	10.2 ± 2.7	9.7 ± 2.9	10.6 ± 2.4	0.27
Sa†	8.6 ± 2.0	8.3 ± 2.3	8.9 ± 1.7	0.35
TDI-derived MPI (%)‡	71 ± 17	71 ± 16	71 ± 18	0.99

Data are given as n (%) or mean ± SD. A, mitral peak A velocity; Aa, peak late diastolic myocardial velocity of mitral annulus; DM, diabetes mellitus; EDT, E-deceleration time; HD, hemodialysis; E, mitral peak E velocity; Ea, peak early diastolic myocardial velocity of mitral annulus; LA, left atrial diameter; LV, left ventricular; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESd, LV end-systolic diameter; PVd, peak velocity of systolic pulmonary venous flow; PVs, peak velocity of diastolic pulmonary venous flow; PVr, peak velocity of atrial reversal flow; Sa, peak systolic myocardial velocity of mitral annulus; TDI-derived MPI, tissue-Doppler derived myocardial performance index. †Average of septal, lateral, anterior and inferior Ea-Aa-Sa velocities. ‡Average of septal, lateral, anterior and inferior MPI values.

Table III. Cox proportional hazard analysis of factors predicting combined endpoint of all-cause death and cardiovascular events requring hospitalization.

	Hazard ratio	95% CI	*p* value
Age	1.006	0.97-1.04	0.74
Gender	1.08	0.44-2.69	0.87
Hemodialysis duration (months)	0.99	0.98-1.01	0.77
LA diameter	1.46	0.52-4.12	0.48
LV EF	0.99	0.92-1.08	0.93
LV mass index	0.99	0.98-1.02	0.63
E/Ea†	1.20	1.03-1.39	0.018
E/Vp	1.27	0.69-2.35	0.45

CI: confidence interval; E: mitral peak E velocity; Ea: peak early diastolic myocardial velocity of mitral annulus; E/Ea: ratio of mitral E to Ea; E/Vp: ratio of mitral E to Vp; LA: left atrium; LV: left ventricular; LV EF: left ventricular ejection fraction; Vp: flow propagation velocity. †Average of septal, lateral, anterior and inferior Ea velocities are calculated.

Discussion

In this study, we analyzed the association between several echocardiographic parameters including indices of LV diastolic function and adverse outcomes in chronic hemodialysis patients with normal LV ejection fraction and without clinically evident cardiovascular disease. Our principle finding was that E/E_a ratio was closely linked to future major events. For each unit increase in the value of E/E_a ratio, there was a 20% increase in the combined endpoint of all-cause mortality and non-fatal cardiovascular events. Among other basal echocardiographic parameters related to diastolic function, E/V_p and LA were significantly higher in the adverse outcome group, but neither of these parameters effectively predicted major events.

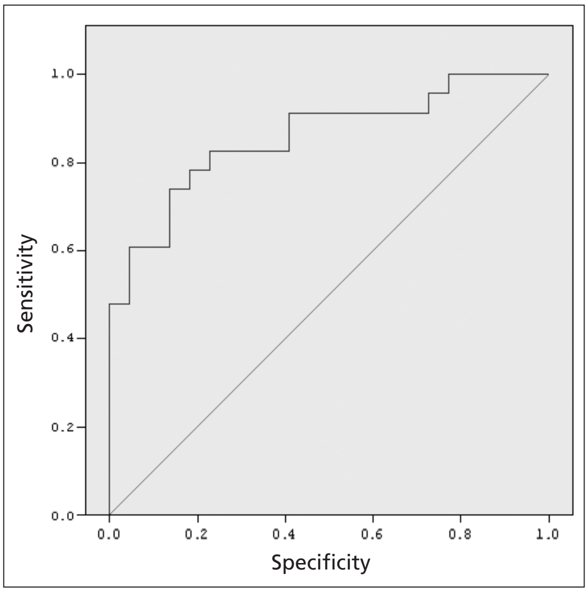

Figure 1. Receiver operator characteristic (ROC) curve demonstrating accuracy of mitral peak Doppler E-wave to average peak early diastolic myocardial velocity of mitral annulus (E/Ea ratio) for predicting combined endpoint of all-cause death and cardiovascular events requring hospitalization. The area under the ROC curve is 0.86 (confidence interval: 0.75-0.97; $p < 0.001$).

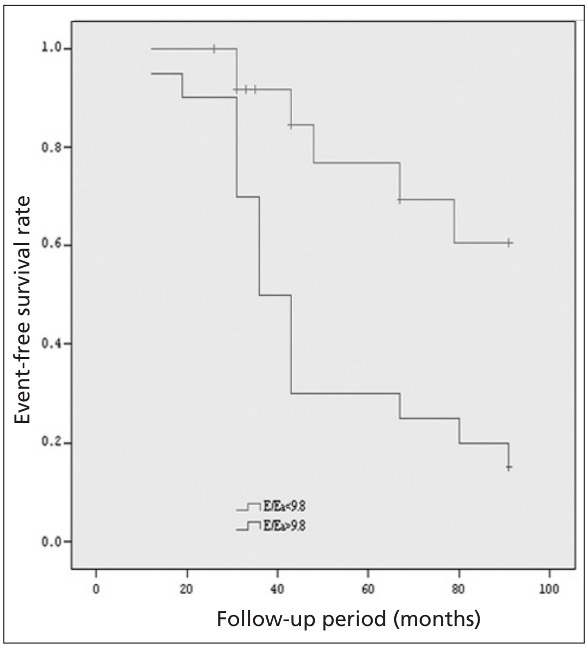

Figure 2. Kaplan-Meier analysis of combined endpoint of all-cause death and cardiovascular events requiring hospitalization. Patients with average E/Ea ratio greater than 9.8 show higher adverse outcome than those with lower E/Ea ratio (log-rank: 9.81; $p = 0.002$).

Presence of LV hypertrophy and systolic dysfunction are increasingly recognized as the strong predictors of cardiovascular mortality in chronic hemodialysis patients[10,22]. However, only very few studies have analyzed the prognostic significance of diastolic dysfunction in chronic hemodialysis patients. Barberato et al[23] reported that approximately every 3 out of 4 hemodialysis patients had diastolic dysfunction. Furthermore, they identifed pseudonormal and restrictive filling patterns of LV as having adverse outcomes regardless of age, gender, diabetes, LV mass and ejection fraction. In one of the three studies investigating the prognostic significance of Doppler echocardiographically derived LV filling pressures in end-stage renal disease, Hsiao et al[24] demonstrated that $E/V_p \geq 1.5$ predicted major events in uremic patients. Other two studies[25,26] suggested E/E_a ratio as a Doppler parameter which accurately predicts the increased mortality in patients with end-stage renal disease. Our findings demonstrating that E/E_a might predict composite of future all-cause mortality and nonfatal cardiovascular events independent from age, gender, hemodialysis duration, LV mass index and LV ejection fraction were consistent with the findings of these two studies.

E/E_a and E/V_p, either seperately or together, have been acknowledged as independent predictors of LV filling pressure, in many circumstances. However, which one is superior to the other as a prognostic risk factor remains unclear. It is a common assumption that E_a and V_p are mainly related to LV relaxation. However, a recent study[27] has shown that these two parameters are not interchangeable for determining LV early diastolic function. In this research, Authors have reported that the inertia force generated by late systolic aortic flow ejected from a left ventricle with good contraction accelerates V_p, along with elastic recoil force which is a consequence of rapid end-systolic unloading of the left ventricle. They have concluded that V_p should not be used as a parameter representing solely relaxation. Furthermore, they have found that E_a was closely correlated with LV relaxation time constant and was a more accurate noninvasive indice of relaxation phase when compared to V_p. Their results are concordant with the findings of previous studies[28,29] indicating E/E_a ratio as a more accurate parameter representing LV end-diastolic pressure (LVEDP) than E/V_p in patients with normal ejection fraction. According to our data, we propose that E/E_a is a more useful parameter to predict future events in chronic hemodialysis patients with normal EF. This result might be explained by the superiority of E_a and E/E_a as parameters representing impaired LV relaxation and increased LVEDP in patients with normal LV ejection fraction, respectively, when compared to the other echocardiographic indices. In ROC curve analysis E/E_a alone with a cut-off value of 9.8 had a sensitivity of 74% and a specificity of 86% to predict major events. 95% CI of area under the curve of P_d (0.75-0.97) did not include 0.5. Therefore, we considered that these predictive values were reliable.[30] This finding is compatible with the report of Rivas-Gotz et al[29] which proposed a cut-off value of 10 for E/E_a as a representative of increased LVEDP, when using averaged E_a values obtained from 4 sites of mitral annulus in patients with normal ejection fraction. Furthermore, the positive and negative likelihood ratios (5.42 and 0.30, respectively) supported the clinical usefulness of E/E_a as a prognostic marker, since it is established that positive likelihood ratios greater than 5 provide reasonable evidence to rule in a diagnosis[31].

Post-mortem and biopsy investigations have revealed that diffuse intermyocardiocytic fibrosis is a dominant feature of structural myocardial remodelling in the uremic patients[8,32]. It might contribute to increased LV stiffness and filling pressure and consequently diastolic dysfunction[8]. Indeed, it has been reported that uremic cardiomyopathy characterized by interstitial cardiac fibrosis can also impair myocardial conduction and predispose to ventricular arrhythmias[32-35]. Even in the abscence of epicardial coronary artery stenosis, impaired LV relaxation is reported to be associated with decreased coronary flow and may lead to myocardial ischemia and consequently LV dysfunction[36,37]. In our study, 15 (65%) of the major outcomes were associated with one of the events including acute heart failure, acute coronary syndrome, sudden cardiac death or documented malign ventricular arrhythmia. Hence, we might suggest that increased LV filling pressure, as assessed by E/E_a ratio, reflects impaired LV relaxation – a functional consequence of myocardial fibrosis which plays a central role in the development of cardiovascular complications in chronic hemodialysis patients.

Left ventricular systolic dysfunction has been reported to be an independent risk factor for cardiovascular mortality in hemodialysis patients. However, our study population consisted of patients with preserved EF, hence there was no significant difference between the groups with and without major event, regarding EF. Furthermore, the peak systolic myocardial velocities which were obtained from the septal, lateral, anterior and inferior aspects of the mitral annulus were compared to examine probable subtle systolic dysfunction. Either peak velocities of the each segments or their average values did not show any significant difference between the patients with and without major outcomes. In our study, we also assessed whether TDI-derived MPI had a predictive value for adverse events. In a previous research performed in our clinics, Ozdemir et al[38] proposed TDI-derived MPI as a Doppler index independent from loading conditions. In their recently published study, Kim et al[39] had also reported that TDI-derived MPI is a reliable index-predicting cardiovascular adverse outcomes in heart failure with preserved ejection fraction. Likewise, our hypothesis was that pathophysiological processes involving myocardium might not solely be restricted to diastolic function, but also systolic abnormalities even in patients with normal segmental motion could be uncovered by this preload independent index. However, there was no significant difference between the groups with and without adverse events.

Our study population differed from the studies mentioned above with many aspects. All the patients had normal functional capacity and LV ejection fraction (>50%) without any wall motion abnormalities by two-timensional echocardiographic evaluation. Subjects with any clinical suspicion of heart failure, coronary artery disease or volume overload were excluded from the study. As far as we know, this is the first study comparing the prognostic role of both systolic and diastolic echocardiographic indices, rather than evaluating the utility of a single parameter for predicting long-term future events. Hence, we believe that prediction of future adverse outcomes in a relatively lower-risk subgroup of chronic hemodialysis patients by means of non-invasive methods would be of clinical value.

Study Limitations

Our study population consisted of clinically stable hemodialysis patients with normal LV EF. Therefore, our results should not be generalized to hemodialysis patients with evident cardiovascular disease and systolic dysfunction.

One of the drawbacks of our study is the fact that, the presence of coronary artery disease was not excluded with non-invasive stress tests, since the participants were asymptomatic. Therefore, contribution of silent myocardial ischemia to adverse outcomes could not be completely eliminated. Regarding left atrial measurements, only diameters obtained from the parasternal long-axis view were measured, although the value of left atrial volume index during the evaluation of diastolic functions is increasingly understood and its use is highly recommended[40]. Despite these limitations, a definite association between E/E_a and future adverse outcomes was observed and this finding was concordant with previous data.

Conclusions

E/E_a might be an accurate echocardiographic index for the prediction of major adverse events during long-term follow-up, allowing the risk stratification of relatively low-risked chronic hemodialysis patients with normal EF and without evident cardiovascular disease.

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