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Association of brain natriuretic peptide and adrenomedullin plasma levels with left ventricular filling pressures in end-stage renal disease patients on hemodialysis

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Abstract. – OBJECTIVE: Adrenomedullin (ADM) and brain natriuretic peptide (BNP) are known to be associated with elevated left ventricular filling pressures. However, little is known about this association in hemodialysis (HD) patients with preserved left ventricular ejection fraction (LVEF). Our objective was to evaluate the potential association between E/e' ratio and plasma levels of BNP and ADM in end-stage renal disease (ESRD) patients with preserved LVEF undergoing chronic hemodialysis.

PATIENTS AND METHODS: The study group enrolled 62 ESRD patients treated with hemodialysis three times weekly. BNP and ADM plasma concentration measurements and echocardiographic examination were performed 30 minutes after hemodialysis. E/e' ratio, evaluated by Tissue Doppler imaging and measured at the basal septum, was used as a surrogate marker for assessing left ventricular filling pressures.

RESULTS: The mean age of patients was 62 ± 25 years. The mean BNP and ADM values after hemodialysis were 0.40 ± 6.73 ng/ml and 0.06 ± 2.12 ng/ml, respectively. Elderly patients with hypertrophied left ventricles and larger left atria displayed higher E/e' values. BNP (r = 0.324. $p = 0.018$) and ADM (r = 0.319, $p = 0.042$) plasma levels were positively and significantly associated with E/e'. Multivariate regression analysis including BNP, ADM, age, hemodialysis duration, left ventricular end-systolic volume index, LVEF, left ventricular mass index and left atrium volume index, revealed that ADM (p-value 0.025) but not BNP levels, were independently associated with the E/e' ratio.

CONCLUSIONS: ADM, but not BNP, was independently associated with septal E/e' in HD patients with preserved LVEF. ADM plasma levels can be used as a surrogate index to assess left ventricular filling pressures in HD patients.

Key Words:
Brain natriuretic peptide, Adrenomedullin, Diastolic dysfunction, Hemodialysis, End-stage renal disease, Biomarkers.

Abbreviations

ADM = Adrenomedullin; ANP = atrial natriuretic peptide; ASE = American Society of Echocardiography; *B* = understandardized beta; BNP = brain natriuretic peptide; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CRIC = Chronic Renal Insufficiency Cohort; DT = deceleration time; E′ = early diastolic velocity; EACVI = European Association of Cardiovascular Imaging; EF = ejection fraction; EIA = Enzyme Immunoassay; ESRD = end stage renal disease; eGFR= estimated glomerular filtration rate; HD = hemodialysis; IVRT = isovolumic relaxation time; IQR = interquartile range; LAVi = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = Left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVEDVi = left ventricular end-diastolic volume index; LVESVi = left ventricular end-systolic volume index; LVMi = left ventricular mass index; LVH = left ventricular hypertrophy; *p* = probability value; PAH = pulmonary artery hypertension; PASP = pulmonary artery systolic pressure; PVa = atrial pulmonary vein flow reversal velocity; PVd = pulmonary vein flow diastolic velocity; PVs = pulmonary vein flow systolic velocity; r = correlation coefficient; PW = pulse wave; R square = square of the correlation coefficient; ROC = Receiver Operating Characteristic; RAVi = right atrial volume index; RV = right ventricular; RVEDD = right ventricular end-diastolic diameter; RVESD = right ventricular end-systolic diameter; SD = standard deviation; SE = standard error; SPSS = Statistical Package for the Social Sciences; Tei index = myocardial performance index; USA= United States of America.

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Introduction

The end-stage renal disease is associated with increased cardiovascular risk, increased incidence of heart failure and mortality[1-4]. Cardiovascular disease is the leading cause of death in patients with advanced chronic kidney disease accounting for about 40% of deaths in international registries[1,3,5].

Echocardiography provides a non-invasive assessment of cardiac structures and function. Diastolic dysfunction is common among hemodialysis patients and is associated with increased mortality and morbidity[6,7]. Therefore, an accurate evaluation of left ventricular (LV) diastolic dysfunction is crucial in the management and risk stratification of hemodialysis patients, especially in those with preserved ejection fraction (EF). Particularly, LV diastolic function and its determinants might represent a vital target for therapeutic strategies focusing on improving the abysmal prognosis of this group of hemodialysis patients with preserved EF[6,7]. Biomarkers, which provide insight into the pathogenesis and predict fatal outcomes are poorly established but eminently needed for early risk stratification of this high-risk cohort of patients[8]. Neurohumoral activation is the general term for the participation of peptides in the regulation of the cardiovascular system[9,10]. Renin, aldosterone, catecholamines (epinephrine and norepinephrine), brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), and adrenomedullin (ADM) are the cardiovascular peptides most commonly involved in neurohumoral activation[9-13]. They play various physiological roles, in particular in the regulation of blood pressure, the volume of body fluids, the proliferation and hypertrophy of myocardial cells[9,10,12,13]. Elevated levels of BNP indicate an increased risk of cardiovascular events and are clinically useful to predict cardiac events in patients with dialysis[9,11]. ADM demonstrates the decompensated reaction to the multifactorial stress state in sustaining the integrity of the cardiovascular system in ESRD[8]. In hemodialysis patients, plasma ADM levels are associated with cardiac dysfunction, systemic inflammation, excessive blood volume, and increased cardiovascular outcomes and mortality[8,13]. Since both peptides increase with deteriorating kidney function, it is unclear whether recently established thresholds can be adapted for prediction of all-cause and cardiovascular mortality in patients with renal disease[8]. The study aimed to correlate the diastolic dysfunction in chronic dialysis patients using biomarkers and to establish an early diagnosis.

Patients and Methods

Patients

This prospective study of 62 hemodialysis patients was performed at AHEPA University Hospital, Thessaloniki, Greece from 2011 to 2014. All participants provided the informed consent, and the study protocol was approved and conducted in accordance with the principles underlined in the Declaration of Helsinki by the respective institutional review boards and the Ethics Committee of the Aristotle University of Thessaloniki School of Medicine. The patients were counseled and explained about the objectives of the study by a qualified medical doctor. Detailed personal medical history was taken using a standard questionnaire. Patients with acute coronary syndromes, pulmonary embolism, pericardial diseases, connective tissue diseases, cancer diseases, and hemodynamically unstable patients during dialysis were excluded from the study.

Laboratory Tests/Assays

Blood samples were taken from all subjects while supine, 30 minutes after dialysis for the assessment of ADM and BNP. Aliquots of the samples were stored at -70°C prior to analysis (storage time: 9 months). Detection of ADM was performed using an enzyme immunoassay kit (ADM EIA kit, Phoenix Pharmaceuticals Inc., Burlingame, CA, USA). The lower detection limit of the assay is 0.13 ng/ml; the assay range is 0-100 ng/ml and the inter-assay coefficient of variance is < 15%. BNP was determined by an enzyme immunoassay kit (BNP-32, Phoenix Pharmaceuticals Inc., Burlingame, CA, USA). The lower detection limit of the assay is 0.26 ng/ml; the assay range is 0-100 ng/ml and the inter-assay coefficient of variance is <15%. Personnel performed laboratory measurements in a blinded fashion without the knowledge of the clinical status of the patient.

Clinical Data

From each patient data on dialysis access, interdialytic weight gain, predialytic systolic and diastolic blood pressure, and time on dialysis were extracted. The patients were evaluated by echocardiography 30 minutes after dialysis. To avoid the influence of operator-dependent factors, all echocardiographic evaluations were performed by the same medically

qualified operator. All patients were examined in the left lateral position with a commercially available ultrasound transducer and equipment (M3s probe, Vivid 7, General Electric Healthcare Company, Milwaukee, WI, USA). The images were digitally stored for off-line analysis (EchoPAC version 110.0.0, General Electric Healthcare Company, Milwaukee, WI, USA). A complete two-dimensional echocardiographic examination and, color, pulse- and continuous-wave Doppler tracings were performed. Using the Simpson's biplane method, LV volumes, and EF were assessed from apical two- and four-chamber views. Left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and septal-posterior wall thicknesses were measured by M-mode in the parasternal long-axis view. As recommended by the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI), several parameters of LV diastolic function were assessed. Transmitral E-wave velocity, late diastolic A-wave velocity and E-wave deceleration time (DT) were measured by applying pulse-wave Doppler (PW-Doppler) at the tip of the mitral leaflets in the four-chamber view. E/A ratio, E wave deceleration time (DT) and isovolumic relaxation time (IVRT). Additionally, pulmonary vein flow velocities such as systolic velocity (PVs), diastolic velocity (PVd) and atrial flow reversal velocity (PVa) were recorded. Tissue Doppler Imaging was recorded with a high frame rate (≥ 100 frames/second) from the apical four-chamber view in order to assess myocardial velocities. Peak annular early diastolic velocity (E') was measured in two annular LV segments (septal and lateral) and averaged to calculate the mean early diastolic velocity. The ratio E/e' was calculated, as a validated estimate of LV filling pressure, and significant LV diastolic dysfunction was defined as E/e' > 15.

Statistical Analysis

Statistical analysis was performed using SPSS 23.0 (Windows Version; IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). Distribution of continuous variables was checked for normality using the Kolmogorov-Smirnov test. Normally and non-normally distributed variables were presented as means ± standard deviation (SD) and medians ± interquartile range (IQR), respectively. Categorical data were illustrated as absolute figures and percentages. For comparison of means and medians between two groups, unpaired Student's *t*-test and Mann-Whitney U test were employed respectively. Bivariate correlations were explored using Pearson and Spearman's rho tests as indicated. Multivariate predictors of continuous and binary variables were identified via stepwise linear regression and forward stepwise Wald logistic regression analysis respectively. The performance of a given continuous parameter, which was tested at various thresholds, in the correct classification of a subject in a two-level state variable was evaluated using Receiver Operating Characteristic (ROC) curves. Optimal cut-off values were identified by plotting sensitivity against specificity of the coordinate points of the ROC curve. For all test results, a p-value of < 0.05 was considered statistically significant.

Results

Patients

Data from 62 end-stage renal disease (ESRD) patients on intermittent renal replacement therapy three times a week were available for analysis. Demographic, clinical, biochemical and echocardiographic characteristics of the study population are presented in Table I. Patients enrolled had a mean age of 61.5 years, and there was a slight predominance of male over female gender (56.5% *vs.* 43.5% respectively). Median time since commencing hemodialysis was approximately 3.5 years. The vast majority, namely more than 90%, of the total cohort, had a history of hypertension and as many as 40% of them had established coronary artery disease. Overall, our patients had non-dilated ventricles while LV systolic function was preserved. Nevertheless, features of left ventricular diastolic dysfunction were quite prevalent. Based on gender-specific cut-off values for left ventricular mass indexed to the individual's body surface area, 74.2% of study participants were classified as having left ventricular hypertrophy (LVH). The presence of any degree of diastolic dysfunction was the norm in our population while 22.6% of them had grade II or worse diastolic dysfunction. This was paralleled by an increased left atrial volume index (LAVi) and echocardiographic evidence of elevated left ventricular filling pressures. Of note, average right ventricular volumes and systolic function were within normal range while the prevalence of pulmonary hypertension was estimated as low as 12.9%.

Univariate Analyses

E/e´ measured at the basal septum was used as a surrogate marker for assessing left ventricular filling pressures. Univariate predictors of E/e' are

Table I. Baseline demographic, clinical, echocardiographic and biochemical characteristics of the study population (n = 62). *or Median ± IQR for non-normally distributed variables.

Variable	Mean ± SD* or n (%)	Variable	Mean ± SD* or n (%)
Demographic		*Echocardiographic*	
Age (years)	61.5 ± 25	LVEDVi (mm/m^2)	43.3 ± 23.7
Gender (M/F)	35/27 (56.5/43.5)	LVESVi (mm/m^2)	19.7 ± 13.1
Dry weight (kg)	68.1 ± 11.6	EF (%)	58.0 ± 10.1
Waist circum. (cm)	95.4 ± 10.1	Cardiac index (L/min/m^2)	2.5 ± 1.1
Hemodialysis (months)	43.0 ± 66.0	LVMi (g/m^2)	149.6 ± 60.4
Clinical		LAVi (mL/m^2)	34.3 ± 23.6
Diabetes mellitus	16 (25.8)	E (m/s)	0.64 ± 0.38
Hypertension	56 (90.3)	E deceleration time (ms)	232.9 ± 64.9
Smoking (current)	14 (22.6)	Sm (septal) (m/s)	0.07 ± 0.02
CAD	25 (40.3)	Sm (lateral) (m/s)	0.08 ± 0.02
LVESD	8 (12.9)	E/e' (septal)	12.4 ± 8.7
LVH	46 (74.2)	E/e' (lateral)	8.0 ± 4.2
Diastolic dysfunction (I/II/III)	31/10/4 (50.0/16.1/6.5)	E/e' (average)	10.9 ± 4.2
RVESD	11 (17.7)	Tei index (septal)	0.60 ± 0.24
PAH	8 (12.9)	Tei index (lateral)	0.63 ± 0.25
Biochemical		RVEDD (mm)	32 ± 7.0
eGFR (mL/min/1.73 m^2)	13.6 ± 4.6	Sm RV (m/s)	0.13 ± 0.04
BNP (ng/ml)	0.40 ± 6.73	RAVi (mL/m^2)	24.9 ±14.4
Adrenomedullin (ng/ml)	0.06 ± 2.12	PASP (mm Hg)	25.9 ± 20.2
		Tei index RV	0.62 ± 0.38

presented in Table II. The mean BNP and ADM values after hemodialysis were 0.40 ± 6.73 ng/ml and 0.06 ± 2.12 ng/ml, respectively. Elderly patients, who are on hemodialysis for a longer period, with hypertrophied left ventricles and larger left atria displayed higher E/e' values. BNP (r = 0.324. p = 0.018) and ADM (r = 0.319, p = 0.042) plasma levels were positively and significantly associated with E/e'.

Multivariate Analyses

Multivariate regression analysis including BNP, ADM, age, hemodialysis duration, left ventricular end-systolic volume index (LVESVi), EF, left atrium volume index (LAVi), and left ventricular mass index (LVMi) revealed that ADM (p-value 0,025) but not BNP levels, were independently associated with E/e' ratio. Left ventricular end-diastolic volume index (LVEDVi) was not included in the model due to the strong correlation with LVESVi (partial correlation coefficient r = 0.898, p < 0.0001) in order to avoid multicollinearity. LVESVi was preferred over LVEDVi as the former is a more volume independent index compared to the latter. ADM but not BNP was the sole biochemical parameter, which carried independent predictive ability of E/e' (septal) in ESRD patients post-renal replacement therapy (Table III).

Table II. Univariate predictors of E/e' (septal).

Variable	Correlation coefficient r	p-value
Age	0.368	0.005
Hemodialysis duration	0.286	0.033
LVEDVi	0.340	0.010
LVESVi	0.278	0.038
EF	-0.247	0.057
LVMi	0.426	0.001
LAVi	0.295	0.027
BNP	0.324	0.018
Adrenomedullin	0.319	0.042

Table III. Multivariate predictors of E/e' (septal) using stepwise linear regression analysis.

Variables	B	SE	Beta	*p*-value	Model R square	*p*-value
Age	0.125	0.050	0.339	0.018		
LVMi	0.025	0.011	0.311	0.028	0.342	0.001
Adrenomedullin	0.112	0.048	0.315	0.025		

Discussion

This is the first study demonstrating that ADM is a predictor of diastolic dysfunction in ESRD patients on hemodialysis. We investigated two cardiovascular peptides that play a role in neurohormonal activation, BNP and, ADM, in a prospective cohort study of incident dialysis patients. We observed that increased concentrations of both peptides were associated with an increased incidence of diastolic dysfunction. Several cross-sectional and prospective studies[14,15] based on echocardiography have demonstrated the association between BNP, left ventricular hypertrophy and overall mortality in hemodialysis patients. Recent large-scale studies[16,17] have also reported the predictive value of BNP in the subsequent development of cardiovascular and renal complications. Liu et al[18] investigated 59 hemodialysis patients with preserved ejection fraction and concluded that plasma BNP might serve as a potential biomarker in diagnosing left ventricular diastolic dysfunction in hemodialysis patients with preserved ejection fraction. Takase et al[19], in a cross-sectional and observational study, showed that elevated BNP levels are predictive of cardiovascular events in patients on chronic maintenance hemodialysis, even in those without apparent heart disorders when they start dialysis. They also demonstrated that left ventricular diastolic dysfunction is associated with increased BNP plasma levels and an increased risk of cardiovascular events in patients on hemodialysis[19]. Additionally, Quiroga et al[20] in a cohort study of 211 hemodialysis patients concluded that NT-proBNP and diastolic dysfunction could identify high-risk patients for cardiovascular events. Furthermore, Yoshihara et al[13] showed that plasma ADM levels in dialysis patients were associated with clinical conditions such as cardiac dysfunction, systemic inflammation, excessive blood volume, and increased cardiovascular outcomes and mortality. Artunc et al[21] also concluded that increased concentrations of mid-regional-pro-ADM in dialysis patients are predictive of mortality. El-Shehaby et al[22] investigated the relationship of increased ADM plasma concentrations with cardiac dysfunction, inflammation, oxidative stress, and volume overload in 80 hemodialysis patients, and found a positive correlation between ADM and mitral E/A wave. In our study, high values of BNP concentrations seem to predict diastolic dysfunction according to the results of our univariate analysis. However, multivariate analysis proved that only high levels of ADM were identified as an independent predictor of diastolic dysfunction. These results suggest that ADM may be a more sensitive indicator of the diastolic dysfunction than BNP in ESRD patients on hemodialysis. Renal insufficiency adversely affects cardiac function, producing a vicious circle in which renal insufficiency impairs cardiac performance, which then leads to further impairment of renal function. As a result, kidney insufficiency is a major determinant of the progression of heart failure, congestion, recurrent decompensation, and hospitalization. The etiology of heart failure in patients is complex, and several factors may be at work in ESRD patients. Cardiovascular disease is the leading cause of death in patients with ESRD[1,23]. ESRD patients treated with hemodialysis, experience a variety of hemodynamic and metabolic abnormalities that alter various LV systolic and diastolic function parameters[24]. Diastolic dysfunction is an abnormality of relaxation, filling, or distensibility of the left ventricle that is associated with augmented cardiovascular mortality[6,25]. The LV diastolic dysfunction provides independent and additional prognostic value for long-term mortality and cardiovascular death in patients with ESRD, above and beyond that of LV mass and LVEF[6]. The assessment of diastolic function by echocardiography has shown a high incidence of abnormalities in chronic dialysis patients[7]. In the CRIC study (stage 2-4 chronic kidney disease), diastolic function was abnormal in 71% of patients[26]. A recent prospective 2-center cohort study[27] of 67 hemodialysis patients investigated the association between left

ventricular remodeling by cardiac magnetic resonance (CMR) and the mechanical and uremic stressors in hemodialysis patients. Ross et al[27] did not report any significant association between left ventricular mass and cardiac biomarkers, highlighting the diagnostic and clinical significance of echocardiography in dialysis patients in the CMR era. Early identification of patients with LV diastolic dysfunction may lead to the development of different treatment strategies and in the selection of patients most likely to benefit from these strategies[6]. Therapies preventing further progression of LVMi, and aortic stiffness might prevent and limit the development of LV diastolic dysfunction[6]. Finally, preventing the development of diastolic dysfunction might also improve outcome and reduce the incidence of cardiovascular death in hemodialysis patients[6,7].

Conclusions

We found that ADM, but not BNP, was independently associated with septal E/e' in HD patients with preserved left ventricular EF and represents a reliable early predictor of diastolic dysfunction in ESRD patients on hemodialysis. However, further studies are needed to document if early diagnosis and treatment of diastolic dysfunction in chronic dialysis patients can potentially lead to improved outcomes.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Foussas SG. Acute coronary syndromes and renal disease. Hellenic J Cardiol 2016; 57: 210-213.
2) Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296-1305.
3) de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LM, Ansell D, Collart F, Finne P, Heaf JG, De Meester J, Wetzels JF, Rosendaal FR, Dekker FW. Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA 2009; 302: 1782-1789.
4) Shamseddin MK, Parfrey PS. Sudden cardiac death in chronic kidney disease: epidemiology and prevention. Nat Rev Nephrol 2011; 7: 145-154.
5) Collins AJ, Foley RN, Herzog C, Chavers B, Gilbertson D, Ishani A, Kasiske B, Liu J, Mau LW, McBean M, Murray A, St Peter W, Guo H, Gustafson S, Li Q, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agodoa L. US Renal Data System 2010 Annual Data Report. Am J Kidney Dis 2011; 57: A8, e1-526.
6) de Bie MK, Ajmone Marsan N, Gaasbeek A, Bax JJ, Groeneveld M, Gabreels BA, Delgado V, Rabelink TJ, Schalij MJ, Jukema JW. Left ventricular diastolic dysfunction in dialysis patients assessed by novel speckle tracking strain rate analysis: prevalence and determinants. Int J Nephrol 2012; 2012: 1-7.
7) Han JH, Han JS, Kim EJ, Doh FM, Koo HM, Kim CH, Lee MJ, Oh HJ, Park JT, Han SH, Ryu DR, Yoo TH, Kang SW. Diastolic dysfunction is an independent predictor of cardiovascular events in incident dialysis patients with preserved systolic function. PLoS One 2015; 10: e0118694.
8) Gouya G, Sturm G, Lamina C, Zitt E, Freistätter O, Struck J, Struck J, Wolzt M, Knoll F, Lins F, Lhotta K, Neyer U, Kronenberg F. The association of mid-regional pro-adrenomedullin and mid-regional pro-atrial natriuretic peptide with mortality in an incident dialysis cohort. PLoS One 2011; 6: e17803.
9) Chrysohoou C, Georgiopoulos G, Kosyfa H, Kotsopoulou Haritou I, Kouvari M, Filippou A, Iosifidis S, Tsiamis E, Aggelopoulos P, Pitsavos C, Tousoulis D. Brain Natriuretic Peptide mediates the prognostic role of renal function towards 10-year cardiovascular mortality in patients with Acute Coronary Syndrome: the HHF study (2006-2016). Hellenic J Cardiol 2018; 59: 110-118.
10) Katayama T, Nakashima H, Furudono S, Honda Y, Suzuki S, Yano K. Evaluation of neurohumoral activation (adrenomedullin, BNP, catecholamines, etc.) in patients with acute myocardial infarction. Intern Med 2004; 43: 1015-1022.
11) Goto T, Takase H, Toriyama T, Sugiura T, Kurita Y, Tsuru N, Masuda H, Hayashi K, Ueda R, Dohi Y. Increased circulating levels of natriuretic peptides predict future cardiac event in patients with chronic hemodialysis. Nephron 2002; 92: 610-615.
12) Nishikimi T. Adrenomedullin in the kidney-renal physiological and pathophysiological roles. Curr Med Chem 2007; 14: 1689-1699.

13) Yoshihara F, Ernst A, Morgenthaler NG, Horio T, Nakamura S, Nakahama H, Nakata H, Bergmann A, Kangawa K, Kawano Y. Midregional proadrenomedullin reflects cardiac dysfunction in haemodialysis patients with cardiovascular disease. Nephrol Dial Transplant 2007; 22: 2263-2268.

14) Zoccali C, Mallamaci F, Benedetto FA, Tripepi G, Parlongo S, Cataliotti A, Cutrupi S, Giacone G, Bellanuova I, Cottini E, Malatino LS; Creed Investigators. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. J Am Soc Nephrol 2001; 12: 1508-1515.

15) Apple FS, Murakami MM, Pearce LA, Herzog CA. Multi-biomarker risk stratification of N-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactive protein, and cardiac troponin T and I in end-stage renal disease for all-cause death. Clin Chem 2004; 50: 2279-2285.

16) Kim Y, Matsushita K, Sang Y, Grams ME, Skali H, Shah AM, Hoogeveen RC, Solomon SD, Ballantyne CM, Coresh J. Association of high-sensitivity cardiac troponin T and natriuretic peptide with incident ESRD: the Atherosclerosis Risk In Communities (ARIC) study. Am J Kidney Dis 2015; 65: 550-558.

17) Mishra RK, Li Y, Ricardo AC, Yang W, Keane M, Cuevas M, Christenson R, deFilippi C, Chen J, He J, Kallem RR, Raj DS, Schelling JR, Wright J, Go AS, Shlipak MG; Chronic Renal Insufficiency Cohort Investigators. Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC]). Am J Cardiol 2013; 111: 432-438.

18) Liu H, Zhang YZ, Gao M, Liu BC. Elevation of B-type natriuretic peptide is a sensitive marker of left ventricular diastolic dysfunction in patients with maintenance haemodialysis. Biomarkers 2010; 15: 533-537.

19) Takase H, Dohi Y, Toriyama T, Okado T, Tanaka S, Shinbo H, Kimura G. B-type natriuretic peptide levels and cardiovascular risk in patients with diastolic dysfunction on chronic haemodialysis: cross-sectional and observational studies. Nephrol Dial Transplant 2011; 26: 683-690.

20) Quiroga B, Villaverde M, Abad S, Vega A, Reque J, López-Gómez JM. Diastolic dysfunction and high levels of new cardiac biomarkers as risk factors for cardiovascular events and mortality in hemodialysis patients. Blood Purif 2013; 36: 98-106.

21) Artunc F, Nowak A, Mueller C, Breidthardt T, Twerenbold R, Wagner R, Peter A, Haering HU, Ebmeyer S, Friedrich B. Plasma concentrations of the vasoactive peptide fragments mid-regional pro-adrenomedullin, C-terminal pro-endothelin 1 and copeptin in hemodialysis patients: associated factors and prediction of mortality. PLoS One 2014; 9: e86148.

22) El-Shehaby AM, El-Khatib MM, Battah AA. Relationship of increased circulating adrenomedullin with cardiac dysfunction, inflammation, oxidative stress and volume overload in hemodialysis patients. Scand J Clin Lab Invest 2011; 71: 208-215.

23) Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003; 108: 2154-2169.

24) Duran M, Unal A, Inanc MT, Esin F, Yilmaz Y, Ornek E. Effect of maintenance hemodialysis on diastolic left ventricular function in end-stage renal disease. Clinics (Sao Paulo) 2010; 65: 979-984.

25) Aggeli C, Tsiamis E, Tousoulis D. Left ventricular diastolic dysfunction: an old, known entity in a technologically modern era. Hellenic J Cardiol 2016; 57: 99-100.

26) Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, Dries D, Xie D, Chen J, He J, Anderson A, Go AS, Shlipak MG; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Associations between kidney function and subclinical cardiac abnormalities in CKD. J Am Soc Nephrol 2012; 23: 1725-1734.

27) Ross BA, Wald R, Goldstein MB, Yuen DA, Leipsic J, Kiaii M, Rathe A, Deva DP, Kirpalani A, Bello OO, Graham JJ, Leong-Poi H, Connelly KA, Yan AT. Relationships between left ventricular structure and function according to cardiac MRI and cardiac biomarkers in end-stage renal disease. Can J Cardiol 2017; 33: 501-507.