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ORIGINAL PAPER

Diastolic dysfunction in asymptomatic hemodialysis patients in the light of the current echocardiographic guidelines

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Abstract

The prevalence of the left ventricular hypertrophy (LVH) is very high in end-stage renal disease treated by hemodialysis. Diastolic dysfunction is a frequent consequence and leads to the development of heart failure with preserved ejection fraction. New American/European echocardiographic guidelines for the assessment of diastolic function simplified the evaluation and were published recently. The aim of this study was to reveal if the new guidelines stratify asymptomatic hemodialysis patients by the levels of brain-natriuretic peptide (BNP). A cohort of 46 patients hemodialyzed in one center with the lack of overt heart failure, systolic dysfunction, arrhythmia or significant valvular disease were examined by echocardiography before and after a single hemodialysis and blood samples for BNP analysis were drawn at both occasions. The LVH was present in 53% of patients, concentric remodeling in another 17%. Higher indexed left ventricular mass was related to higher BNP levels ($r = 0.58$, $p = 0.0001$). Before hemodialysis, diastolic dysfunction was present in 61%: grade 1 in 25%, grade 2 in 21% and grade 3 in 8%. The higher grade of diastolic dysfunction was associated with the incremental increase of BNP. The post-dialysis echocardiography did not allow the assessment of diastolic function in as many as 37% of patients. Our study has shown that the application of the current guidelines for the assessment of diastolic function based on simple four criteria differentiate hemodialysis symptomless patients with preserved systolic function according to BNP levels. BNP levels also rose together with the left ventricular mass. The ratio E/e′ medial seemed to be a better predictor of increased BNP than E/e′ lateral or E/e′ averaged.

Keywords Chronic kidney disease · Heart failure · Diastolic dysfunction · Hemodialysis · Echocardiography

Introduction

Vast majority of patients with end stage renal disease (ESRD) suffer and die from cardiovascular complications. Many mechanisms are involved and include arterial disease—coronary artery disease, left ventricular hypertrophy (LVH), accelerated valvular degeneration leading to either stenotic or regurgitant valvular heart disease etc. [1]. LVH is very frequent in ESRD patients and the left ventricular mass index further progressively increases after the beginning of hemodialysis therapy [2, 3]. Responsible factors include arterial hypertension, cyclic volume overload, but also hyperkinetic circulation as the result of anemia, dialysis arteriovenous access and water retention. The presence of LVH prolongs isovolumic relaxation time and decreases left ventricular compliance—two determinants of diastolic dysfunction. Diastolic dysfunction is the main characteristics of the heart failure with preserved left ventricular ejection fraction (HFpEF)—an extensively studied entity responsible for the majority of manifest heart failure at ESRD patients [4].

Diastolic (dys)function is clinically examined especially by echocardiography. Many indices of diastolic function have been described, making the assessment too complex. New American/European recommendations for the evaluation of left ventricular diastolic function have been published in 2016 [5]. These guidelines simplify the assessment of diastolic function, which is now mainly based on four parameters: (1) transmitral flow analysis; (2) relation of the early filling and early movement of mitral annulus velocities;

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(3) left atrial size; and (4) peak gradient of tricuspid regurgitation. However, ESRD patients possess several limitations of this approach: early left ventricular filling depends on the hydration status (and thus on the delay from hemodialysis), left atrium dilated frequently due to water overload and pulmonary hypertension of combined etiology is common in this population [6]. Moreover, left atrial systolic dysfunction develops with chronic hemodialysis therapy [7]. Therefore, diastolic function is not assessed in some centers, but rather expected in practically all ESRD patients.

The levels of B-type natriuretic peptide (BNP) are used not only for the diagnosis of heart failure [8], but also as an independent marker of heart failure compensation and even for the estimation of ideal dry weight of ESRD patients [9], although this attempt has been criticized [10]. At least in pediatric hemodialysis patients, chronically increased BNP levels were related to higher mortality [11].

HFpEF is being intensively investigated nowadays and impaired kidney function is one of the suspect mechanisms even in milder stages of chronic kidney disease [12]. It has been shown that HFpEF is very common in ESRD patients, although its diagnosis is tricky since it manifests in the same manner as simple water overload, frequent in this population. Moreover, many dialysis patients are frail and also have orthopedic limitations, so the complaints of heart failure symptoms are not often.

Therefore, we performed a single center study of ESRD patients with no clinical signs of heart failure treated by chronic hemodialysis at our Institution to reveal if the new guidelines stratify these patients [5] by the levels of BNP. Moreover, we examined, how does the assessment of diastolic function change after a single hemodialysis.

Materials and methods

A cohort of hemodialysis patients, who regularly come for hemodialysis therapy into our Institution, was asked to participate in this study. The patients were included only if they were clinically stable, without clinical signs of heart failure, without any acute disease, if they had appropriate acoustic windows for echocardiography and were hemodialyzed three times a week. The exclusion criteria included the history of manifest coronary artery disease, moderate-to-severe valvular disease, HFpEF $<45\%$, history of lung disease, history of established congestive heart failure and history of atrial fibrillation. The study conforms to the Declaration of Helsinki and has been proven by the local Ethical committee. The patients were enrolled after explanation of study principles and signing of the informed consent.

Patients came to their regular hemodialysis session. No special intervention was made prior to the dialysis session to improve the patient´s habits regarding their compliance to drinking restrictions or medication. We also did not change the setting of the dry weight for purpose of this study. Before the start of hemodialysis, we left the patient relaxed in supine position for at least 20 min. Then, before the start of dialysis, echocardiography and ultrasonographical vascular access flow volume calculation were recorded. The same records were obtained at the end of hemodialysis—before the patient verticalized.

Blood was drawn just after the beginning and before the end of dialysis from the extracorporeal circuit. Blood samples were placed in ethylenediamintetraacetic acid anticoagulated tubes and plasma BNP levels were analyzed within 1 h using the chemiluminescent immunoassay (Bayer, Germany).

Heart rate, blood pressure and patient´s weight were recorded before and after hemodialysis.

Echocardiography and ultrasonography were recorded using the Vivid Q (General Electric, USA) portable system and stored digitally in raw data format as video loops. The records were analyzed using the EchoPAC working station offline by one experienced echocardiographer and ultrasonographer. The left ventricular indices (end-diastolic and end-systolic internal volumes—LVEDV and LVESV, left ventricular mass indexed to body surface area—LVMI) and the left atrial volume were measured according to the guidelines of the American Society of Echocardiography and European Association for Cardiovascular Imaging [13].

The left ventricular diastolic function was assessed according to the recent Euro–American recommendations [5]: the early (E) and late (atrial—A) peaks of the left ventricular filling were recorded from the transmitral flow. Then we recorded the tissue Doppler velocity analysis of the septal and lateral parts of the mitral annulus. Left atrial volume index and peak tricuspid regurgitant velocity were also measured.

Vascular access flow volume (Qa) was measured in brachial artery using duplex Doppler ultrasonography method described previously [14] by the same ultrasound device (Vivid Q) using a linear array ultrasound probe.

Statistical methods

Data is presented as mean $\pm$ SD. The measured BNP values were logarithmically transformed to get Gaussian distribution for analysis; the original BNP results are presented as median. The pre- and post-dialysis results were compared by the paired *t* test, comparisons of patients with and without diastolic dysfunction by unpaired *t* test. Non-parametric variables (BNP) were expressed as median(quartile range-QR) and its change by hemodialysis was calculated by the Wilcoxon matched pairs test. Correlation analysis was performed according to Pearson; BNP was logarithmically transformed prior to the analysis to get Gaussian

distribution. The p-value <0.05 was considered significant for differences and $p<0.01$ for the correlation analysis. All calculations were performed using the STATISTICA software, version 12 (StatSoft, USA).

Results

We included 46 patients suffering from ESRD (23 males, 23 females), aged 62 ± 15 years, treated by chronic hemodialysis for 61 ± 52 months. The most common causes of ESRD were as follows: diabetes mellitus (17%), arterial hypertension (17%), polycystic kidney disease (17%) and IgA nephropathy (15%). The LVH was present in 53% of patients (eccentric in 30% and concentric hypertrophy in 23%), concentric remodeling in another 17%. Higher LVMi was mirrored by higher BNP levels ($r=0.58$, $p=0.0001$)—see Fig. 1.

Before hemodialysis, diastolic dysfunction defined by the current guidelines was present in 54%: grade 1 in 25%, grade 2 in 21% and grade 3 in 8%. In 3 (7%) patients the estimation of diastolic function was not possible by the classic four parameters (50% positive, 50% negative). In all three of them, the diastolic dysfunction was probable based on the combination of left atrial dilatation and LVH—the attempt also recommended by the guidelines. The higher grade of diastolic dysfunction was associated with the incremental increase of BNP (Fig. 2). Blood pressure was not significantly different among normal diastolic function and diastolic dysfunction grades. Patients with any grade of diastolic dysfunction were older than those with normal diastolic function (66.0 ± 11.2 vs. 52.6 ± 15.7, $p=0.003$).

Any grade of diastolic dysfunction was linked to higher left ventricular mass index (114.3 ± 26.5 vs. 91.6 ± 23.3 g/m^2 in patients without diastolic dysfunction, $p=0.02$). However, there was only trend of the relation between LVMi and E/e′ medial: $r=0.29$, $p=0.08$.

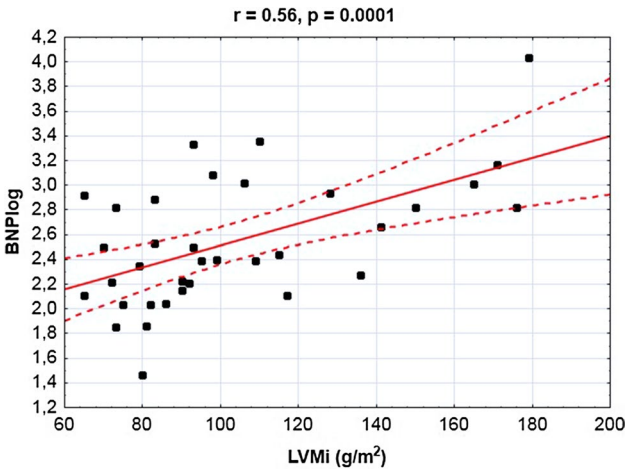

Fig. 1 Relation between the indexed left ventricular mass and BNP. BNP was logarithmically transformed to get Gaussian distribution

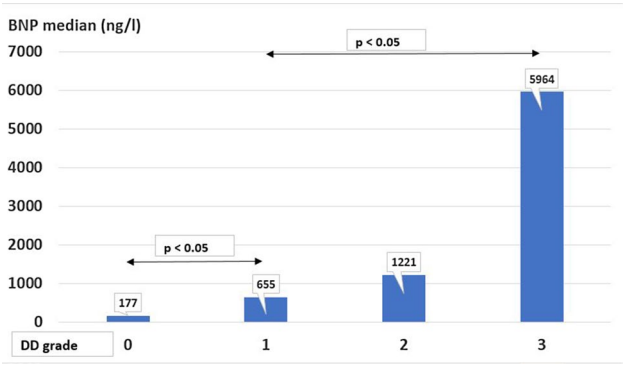

Fig. 2 BNP levels among diastolic dysfunction grades. 0 = no diastolic dysfunction; The numbers at x axis show the grade of diastolic dysfunction. Median values of BNP levels are above the columns. The difference of BNP levels was statistically significant in comparison between (1) no diastolic dysfunction versus grade 1; (2) grade 1 and grade 3

Table 1 documents univariate analysis between individual diastolic function parameters and BNP levels. Only tissue Doppler velocity analysis from the medial part of the mitral annulus (e′ and related E/e′) was significantly related to BNP levels (opposed to e′ and E/e′ lateral).

Growing grade of diastolic dysfunction was accompanied by incrementally increased BNP levels—see Fig. 2. In this selected group of patients with (almost) normal left ventricular systolic function, the BNP levels were not significantly related to ejection fraction.

After hemodialysis, there was evident decrease especially of E-wave and of the left atrial size—see Table 2 for details. However, the diastolic function was not possible to assess in as many as 17 (37%) patients after hemodialysis. The main

Table 1 Relation of BNP level to individual markers of diastolic function

	r-value	p-value
E-wave	0.22	0.21
E/A	**0.41**	**0.02**
e′med	**−0.46**	**0.007**
e′lat	**−0.38**	**0.03**
E/e′med	**0.56**	**0.001**
E/e′lat	0.25	0.15
E/emean	**0.45**	**0.007**
LAVi	**0.45**	**0.02**
Max. velocity of tric. reg.*	0.21	0.40

Significant relation is bold

*Tricuspid velocity was measurable in only 53% of patients

Table 2 Changes of diastolic function determinants by hemodialysis

	Before HD	After HD	p-value
BP systolic (mmHg)	140.3 ± 22.5	123.2 ± 27.4	**0.002**
BP diastolic (mmHg)	74.5 ± 16.6	66.5 ± 13.1	**0.001**
Heart rate (/min)	74.5 ± 14.7	79.1 ± 16.1	**0.004**
E-wave (m/sec)	103.4 ± 35.1	87.1 ± 39.2	$<\mathbf{10^{-4}}$
A-wave (m/sec)	91.9 ± 34.7	94.3 ± 36.1	0.61
E/A	1.3 ± 0.9	1.0 ± 0.6	**0.045**
e′med (cm/sec)	8.0 ± 3.4	7.4 ± 3.1	0.17
a′med (cm/sec)	9.3 ± 3.2	10.6 ± 4.2	**0.02**
E/e′med	15.1 ± 8.1	15.1 ± 13.5	0.96
LAVi (mL/m^2)	39.4 ± 12.6	31.4 ± 15.8	**0.00003**

Bold represents the significant values of $p < 0.05$

BP blood pressure, *HD* hemodialysis, *LAVi* left atrial volume indexed to body surface area

reason was the worsening of visibility and disappearance of tricuspid regurgitation. BNP decreased by hemodialysis from 338 (QR 841) to 291 (QR 618) ng/L.

Discussion

Our study has shown that the application of the current guidelines for the assessment of diastolic function based on simple four criteria differentiate hemodialysis symptomless patients with preserved systolic function according to BNP levels. BNP levels also rose together with the left ventricular mass. The ratio E/e′ medial seemed to be a better predictor of increased BNP than E/e′ lateral or E/e′ averaged. After hemodialysis, the assessment of diastolic function was not possible in many patients especially due to poorer visibility and disappearance of tricuspid regurgitation.

The high frequency of diastolic dysfunction in chronic dialysis patients has been attributed especially to the high frequency of LVH and cyclic water overload. The diastolic dysfunction is significantly more frequent heart failure mechanism than reduced ejection fraction in this population [4, 14]. Our study differs by testing asymptomatic patients and by implementation of the recent echocardiographic guidelines for the assessment of diastolic function. Our data show that diastolic dysfunction is frequent in dialysis population and its grades are linked to higher BNP levels and thus to clinically silent heart failure. Data from the general population also comes from patients having shortness of breath and other signs of HFpEF [15]. Interestingly, renal retention of sodium and water due to impaired glomerular filtration and neurohumoral activation overload is a common feature also in HFpEF patients without established chronic kidney disease [16]. Although ESRD patients differ significantly, the cyclic hydration changes are typical for hemodialysis therapy and represent probably a common mechanism.

The current guidelines [5] recommend collection of the tissue Doppler imaging data from both medial and lateral part of mitral annulus and using the average of both values. They also state that less data is available for the medial part of mitral annulus. This practice does not seem to be advisable in ESRD patients according to our data, where the relation between e′ medial and E/e′ medial with BNP was more robust than those for e′ lateral. The most probable explanation is that the annular calcification usually begins in the lateral part of the mitral annulus and, sometimes, it even spreads to the adjacent myocardium. Thus, the limited movement of the lateral part of mitral annulus documents rather more pronounced local decrease of left ventricular compliance than impaired global diastolic function. Impaired global left ventricular compliance and prolonged relaxation time are two components of the diastolic dysfunction and results of LVH.

High prevalence of LVH was obvious also in our study. Only 22% of our patients had normal left ventricular geometry. The relation between left ventricular mass index and (logarithmized) BNP levels was almost linear (Fig. 1) similarly to the results of other studies [17, 18]. LVH is known to be associated with increased mortality [19] and develops due to many factors in ESRD patients, such as cyclic overhydration, hypertension, increased aortic and arterial stiffness etc. Interestingly, the development of LVH is accelerated by fibroblast growth factor-23 and other molecules responsible also for cardiovascular calcifications. Histologically, LVH of ESRD patients differs from the general population by more advanced disperse fibrotization and capillary rarefaction [20]. Such changes explain the high incidence of the diastolic dysfunction.

Ultrafiltration during hemodialysis led especially to the decrease of E-wave and of the left atrial size—these two parameters are thus most volume-dependent. It was mirrored by the decrease of BNP-levels. However, it was not possible to estimate the diastolic function in more than one-third of patients after hemodialysis especially due to worse visibility and diminished tricuspid regurgitation. This observation underlines the recommendation to perform echocardiography (at least) 24 h after the previous hemodialysis and to record the time delay.

In conclusion, diastolic dysfunction is very frequent in ESRD patients and to LVH and to increased BNP levels. These connection underline frequent presence of (asymptomatic) HFpEF in ESRD population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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