

Cardiac remodeling and right ventricular function in patients with end-stage renal disease one year since maintenance hemodialysis initiation

Przebudowa serca oraz funkcja prawej komory u pacjentów ze schyłkową niewydolnością nerek rok po włączeniu hemodializoterapii

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Abstract

Introduction. Due to the increasing number of patients requiring renal replacement therapy and bidirectional interactions between kidneys and heart, known as reno-cardiac syndrome, the assessment of dialysis influence on heart performance has become paramount.

Material and methods. This was a prospective study analyzing data of 22 adult patients with end-stage renal disease, referred for maintenance hemodialysis (HD) at our Dialysis Centre between January 2019 and December 2019.

Results. The median age of the patients was 59.5 (51–64) years, and 55% of the study group were females. The most common comorbidities were hypertension (86%) and diabetes (36%). At one-year follow-up, there was a significant decrease in proximal and distal right ventricular outflow tract (RVOT) dimensions ($p = 0.04$; $p = 0.007$ respectively) and in isovolumic acceleration time corrected ($p = 0.01$). As the result of the prolongation of isovolumic relaxation time corrected ($p < 0.001$) and isovolumic contraction time corrected ($p < 0.001$) a significant increase in myocardial performance index (MPI) ($p < 0.001$) was observed.

Conclusions. In patients with end-stage renal disease long-term HD negatively impacts RV function. Isovolumic acceleration and MPI measured with pulsed tissue Doppler are sensitive indicators of changes in RV function.

Key words: echocardiographic assessment, end-stage renal disease, dialysis, right ventricular function

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Introduction

End-stage renal disease (ESRD), defined as the estimated glomerular filtration rate below 15 mL/min/1.73m², is a growing problem around the world due to the rising life expectancy and widespread civilization diseases leading

to kidney function deterioration. Current projections indicate that by 2030 the ESRD population requiring renal replacement therapy, the most prevalent of which remains hemodialysis (HD), may reach over 5 million [1].

Cardiovascular diseases are the leading cause of death in ESRD patients. There is a strong bilateral relationship

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between renal and heart function known as a reno-cardiac syndrome. Renal failure is one of the leading comorbidities that require adequate management in the overall strategy to retard the developing heart failure [2].

Left ventricular (LV) dysfunction is an acknowledged causality factor of adverse clinical outcomes [3]. Recently the significance of right ventricular (RV) function has been highlighted [4]. Particular attention was given to dialyzed patients. Hemodialysis is associated with increased risk of pulmonary hypertension, a condition that has a negative effect on right ventricular structure and function and is recognized as a predictor of mortality in these patients [5].

Echocardiography (ECHO) is the most commonly used cardiac imaging modality competent in recognizing subclinical myocardial abnormalities of both LV and RV. There are reports showing that conventional ECHO, which is easily repetitive and widely accessible, remains accordant with novel methods like two-dimensional speckle tracking ECHO [6] or cardiac magnetic resonance (CMR) imaging [7].

The aim of the study was to investigate whether the HD implementation worsens RV function detectable by conventional echocardiographic methods. Uncovering subclinical RV myocardial abnormalities might help to identify endangered patients and therefore optimize and individualize therapy.

Material and methods

Study design and population

Out of ESRD patients referred for maintenance HD (3 times per week) at the Dialysis Station in Central Clinical Hospital in Lodz 30 consecutive patients in the period from January 2019 to December 2019 were initially selected for the prospective echocardiographic study focused on RV function. Exclusion criteria were: indication for acute HD, severe valvular disease, atrial fibrillation, severe pulmonary hypertension, LV systolic dysfunction, and poor acoustic window for ECHO.

Clinical and echocardiographic examination and blood tests were performed before HD initiation and 12 months later (11.3 ± 0.2 months). Eight patients were lost to follow-up: 6 patients have withdrawn from the study for personal or social reasons (including COVID-19 pandemic fear) and 2 patients died. Finally, data from 22 patients were analysed.

Each patient was completely informed of the purpose and procedure of the study and provided written informed consent. The study was performed in compliance with the Helsinki Declaration and with Good Clinical Practice standards and was approved by the local Bioethical Committee (RNN/135/17/KE, 11/04/2017r).

Echocardiographic examination

The patients underwent transthoracic echocardiographic examinations with conventional, Doppler, and pulsed tissue Doppler imaging (TDI) using ultrasonography Vivid E95 system with S4 probe and simultaneous ECHO recording.

Transthoracic echocardiographic examinations were performed within 24 hours after completion of the second thrice-weekly HD (midweek HD). It allowed achieving optimal dry weight to avoid volume overload that might interfere with cardiac time intervals and overestimate pulmonary pressures. As the heart rate influences the duration of cardiac time intervals all the time measurements were corrected for heart rate according to the following formula: x/\sqrt{RR} interval. Echocardiographic measurements were obtained by the same physician and consecutive 3-beat averaged values were reported.

Standard echocardiographic examination was performed according to the recommendations of the Working Group on Echocardiography of the Polish Cardiac Society [8]. Additionally, several RV morphology and function measurements and calculations were made according to the guidelines endorsed by the European Association of Echocardiography and the American Society of Echocardiography [9, 10]. Pulsed tissue Doppler traces at the tricuspid annulus on RV free wall were used to obtain velocities and cardiac time intervals (Figure 1). The analysed RV parameters included:

1. The RV and right atrium dimensions measured at end-diastole from a RV-focused apical 4-chamber view;
2. RV fractional area change (FAC) obtained by tracing the RV endocardial border at end-diastole and end-systole from the apical 4-chamber view;
3. Tricuspid annular plane systolic excursion (TAPSE);
4. RV systolic longitudinal myocardial tissue velocity (S');
5. RV isovolumic acceleration (IVA) calculated by dividing the peak isovolumic myocardial velocity at isovolumic contraction by the time from the onset to peak velocity measured at the lateral tricuspid annulus;
6. Cardiac time intervals:
 - isovolumic contraction time (IVCT): from the end of the a' wave to the beginning of the s' wave,
 - ejection time: from the beginning of the s' wave to the end of the s' wave,
 - isovolumic relaxation time (IVRT): from the end of the s' wave to the beginning of the e' wave;

An active myocardial relaxation plays a predominant role in RV filling pattern. IVRT duration is affected by systolic pulmonary pressure (sPAP), right atrial pressure and heart rate. Elevated sPAP delays the opening of tricuspid valve which results in prolongation of IVRT while increased right atrial pressure leads to a premature opening of the tricuspid valve and shortening of IVRT.

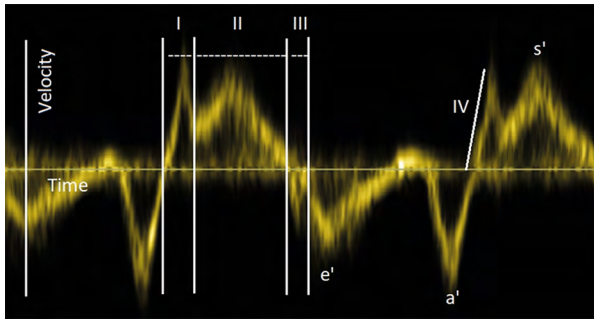


Figure 1. Velocities and cardiac time intervals obtained by pulsed tissue Doppler trace at the tricuspid annulus on the right ventricular free wall; I) isovolumic contraction time; II) ejection time; III) isovolumic relaxation time; IV) isovolumic acceleration; a' – late diastolic tricuspid annular velocity; e' – early diastolic tricuspid annular velocity; s' – peak systolic tricuspid annular velocity

7. RV myocardial performance index (MPI) – an index of global RV performance was calculated using the formula $MPI = (IVCT + IVRT) / \text{ejection time}$.

It is worth mentioning that echocardiographic assessment of the duration of the cardiac time intervals may be performed with the use of conventional pulse wave Doppler, however, measurements performed with pulsed wave TDI are less affected by heart rate, preload, and severity of tricuspid regurgitation and allow simultaneous measurement of both the diastolic and systolic intervals in the same cardiac cycle.

Laboratory measurements

Fasting blood samples for routine measurements including N-terminal pro-brain natriuretic peptide (NT-proBNP) were taken at baseline and at follow-up on the same day as echocardiographic examination (the day after the midweekly HD).

Statistical analysis

All the data from the study were analyzed using STATISTICA 13.3 software (TIBCO, Palo Alto, CA, USA). Qualitative data were shown as numbers, values, and percentages. In order to compare qualitative variables, Chi-squared test was performed and small samples were tested using Fisher's exact test. Continuous variables were reported as median with interquartile ranges (25–75 percentile). Normality was checked using the Shapiro-Wilk test. Comparisons between values before and after HD initiation were made with Wilcoxon signed-rank test. Statistically significant differences are graphically presented on diagrams.

Table 1. Baseline characteristics of the study group

Variable	Study group (n = 22)
Age [years]	59.50 (51–64)
Female, n (%)	12 (55)
BMI [kg/m ²]	28.84 (24.62–33.56)
Diabetes mellitus, n (%)	8 (36)
Smoking, n (%)	5 (23)
Hypertension, n (%)	19 (86)
Creatinine [μmol/L]	588.20 (469.40–731.00)
Urea [mmol/L]	18.52 (14.98–26.75)
Hb [g/dL]	11.35 (10.30–12.40)

Continuous variables are expressed as median (interquartile range [IQR]) and categorical variables as number (percentage); BMI – body mass index; Hb – hemoglobin

Results

Baseline clinical, biochemical and echocardiographic characteristics of 22 ESRD patients who have initiated the maintenance HD is presented in Table 1. RV and LV structure and function parameters at baseline and follow-up are shown in Table 2 and Table 3, respectively.

Right ventricular dimensions, systolic and diastolic function were within normal limits both at baseline and follow-up. There was a tendency to reduction in RV diameters during observation period. Significant reduction was observed with regard to the right ventricular outflow tract (RVOT) proximal and distal diameter ($p = 0.04$; $p = 0.007$, respectively) (Figure 2, Table 2) and in the value of IVA ($p = 0.01$) (Figure 3, Table 2). Significant increase in IVRTc ($p < 0.001$) and IVCTc ($p < 0.001$) and consequently in MPI ($p < 0.001$) was noted (Figure 4, Table 2). No significant changes in LV were shown at follow-up.

Discussion

There is a well-established high prevalence of cardiovascular morbidity and mortality in ESRD patients early after HD initiation [11]. Some of the potential causes are linked to changes in cardiac structure and function.

RV is designed to work in a low-pressure system and its adaptability properties are limited. It has been shown that arteriovenous fistula (AVF) for dialysis access results in the AVF-dependent volume overload that induces RV dysfunction, which affects LV function via ventricular interdependence. In HD patients the cumulative impact of AVF shunt, uremia, fluid retention, renal anemia, and inflammation affects RV performance [12]. The influence of HD

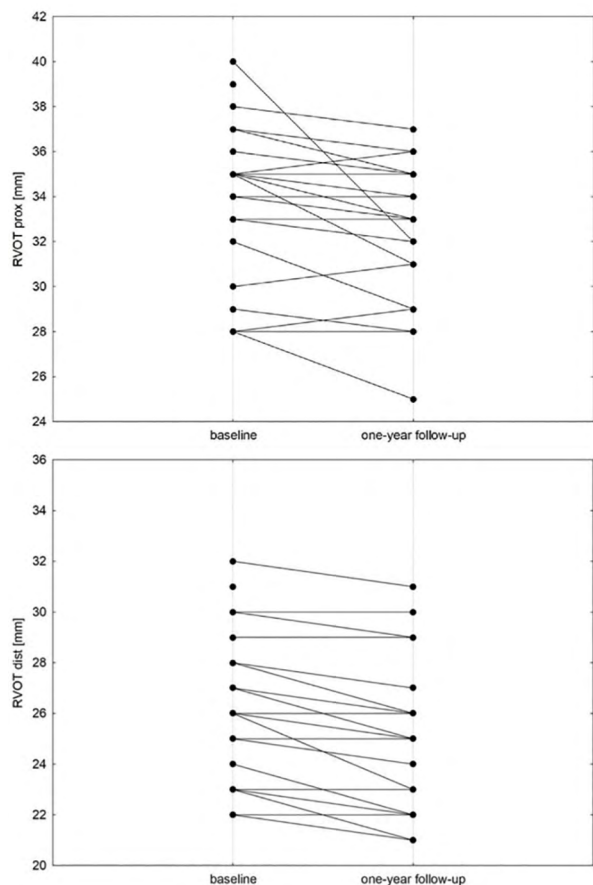


Figure 2. Right ventricular outflow tract proximal (RVOTprox) and distal (RVOTdist) diameter at baseline and one-year follow-up

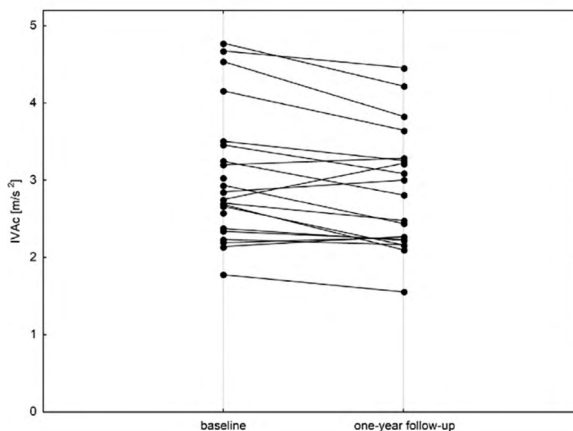


Figure 3. Isovolumic acceleration time corrected for heart rate (IVAc) at baseline and at one-year follow-up

on RV dysfunction and its contribution to increased cardiovascular events is associated with deep uncertainties and the data concerning identification of early RV malfunction indices are scarce. There are studies assessing short term changes of RV parameters e.g. TAPSE, S', FAC, MPI, before and after a single HD procedure, that show improvement of RV function associated with preload reduction [13].

In our group of patients, the proximal and distal right ventricular outflow tract (RVOT) dimensions were significantly lower at follow-up transthoracic echocardiographic examinations whereas diastolic and systolic RV area and FAC

Table 2. Right ventricular structure and function parameters at baseline and one-year follow-up

Parameter	Baseline	Follow-up	p-value
RAA [cm ²]	15.65 (13.70–17.10)	16.30 (13.20–19.00)	0.67
FAC [%]	0.47 (0.40–0.57)	0.47 (0.40–0.58)	0.99
RV _{basal} [mm]	36.00 (34.00–37.00)	35.00 (32.00–43.00)	0.24
RV _{mid} [mm]	30.00 (25.00–34.00)	27.00 (23.00–33.00)	0.82
RV _{long} [mm]	61.00 (55.00–67.00)	60.50 (54.00–69.00)	0.12
RVOT _{prox} [mm]	34.00 (30.00–35.00)	32.50 (29.00–35.00)	0.04
RVOT _{dist} [mm]	26.00 (24.00–28.00)	25.00 (23.00–27.00)	0.007
TR V _{max} [m/s]	2.28 (2.10–2.50)	2.30 (2.10–2.50)	0.77
SPAP [mm Hg]	24.00 (21.00–29.00)	25.00 (20.00–28.00)	0.71
IVRTc [ms]	69.29 (57.98–80.83)	82.62 (72.18–98.07)	< 0.001
IVCTc [ms]	67.41 (58.33–81.06)	76.08 (64.4–87.81)	< 0.001
ETc [ms]	317.43 (302.45–335.35)	322.91 (304.92–347.83)	0.29
MPI	0.44 (0.38–0.50)	0.49 (0.45–0.58)	< 0.001
IVAc [m/s ²]	2.80 (2.37–3.51)	2.69(2.24–3.29)	0.01
TAPSE [mm]	27.00 (25.00–30.00)	25.00 (24.00–28.00)	0.65
S' [cm/s]	14.00 (12.00–15.30)	12.75 (11.00–15.00)	0.17
AcTc [ms]	122.28 (111.26–142.49)	121.55 (112.58–137.68)	0.83

AcTc – pulmonary artery acceleration time corrected for heart rate; ETc – ejection time corrected for heart rate; FAC – fractional area change; IVAc – isovolumic myocardial acceleration corrected for heart rate; IVCTc – isovolumic contraction time corrected for heart rate; IVRTc – isovolumic relaxation time corrected for heart rate; MPI – myocardial performance index; RAA – right atrial area; RV_{basal} – right ventricular basal diameter; RV_{long} – right ventricular longitudinal diameter; RV_{mid} – right ventricular mid-cavity diameter; RVOT_{dist} – distal diameter of right ventricular outflow tract; RVOT_{prox} – proximal diameter of right ventricular outflow tract; S' – tricuspid annular systolic velocity; SPAP – systolic pulmonary arterial pressure; TAPSE – tricuspid annular plane systolic excursion; TR V_{max} – maximal velocity of tricuspid regurgitation

Table 3. Left ventricular structure and function parameters and NT-proBNP at baseline and one-year follow-up

Parameter	Baseline	Follow-up	p-value
EF _{LV} [%]	61.00 (56.00–65.00)	58.50 (55.00–65.00)	0.11
LVDD [mm]	51.00 (48.00–56.00)	49.50 (46.00–53.00)	0.08
TDI e' _{LV} [cm/s]	7.50 (5.60–8.00)	6.85 (4.50–8.50)	0.10
E/e' _{LV}	9.48 (6.88–12.73)	10.20 (10.20–8.82–12.36)	0.19
LAVI [mL/m ²]	36.50 (29.00–49.00)	38.50 (28.00–48.00)	0.25
D1 [mm]	51.00 (48.00–54.00)	49.00 (45.00–54.00)	0.04
D2 [mm]	50.00 (48.00–54.00)	50.00 (47.00–54.00)	0.41
D2/D1	1.00 (0.96–1.02)	1.02 (0.98–1.07)	0.64
NT-proBNP [pg/mL]	2 744.00 (926.60–10 416.00)	2 579.00 (818.40–10 950.00)	0.88

D1 – left ventricular short-axis diameter perpendicular to the septum; D2 – left ventricular short-axis diameter parallel to the septum; D2/D1 – eccentricity index; E/e'_{LV} – early mitral inflow velocity and mitral annular early diastolic velocity ratio; EF_{LV} – left ventricular ejection fraction; LAVI – left atrial volume index; LVDD – left ventricular diastolic dimension; NT-proBNP – N-terminal pro-brain natriuretic peptide; TDI e'_{LV} – tissue Doppler-derived mean early diastolic mitral annulus velocity

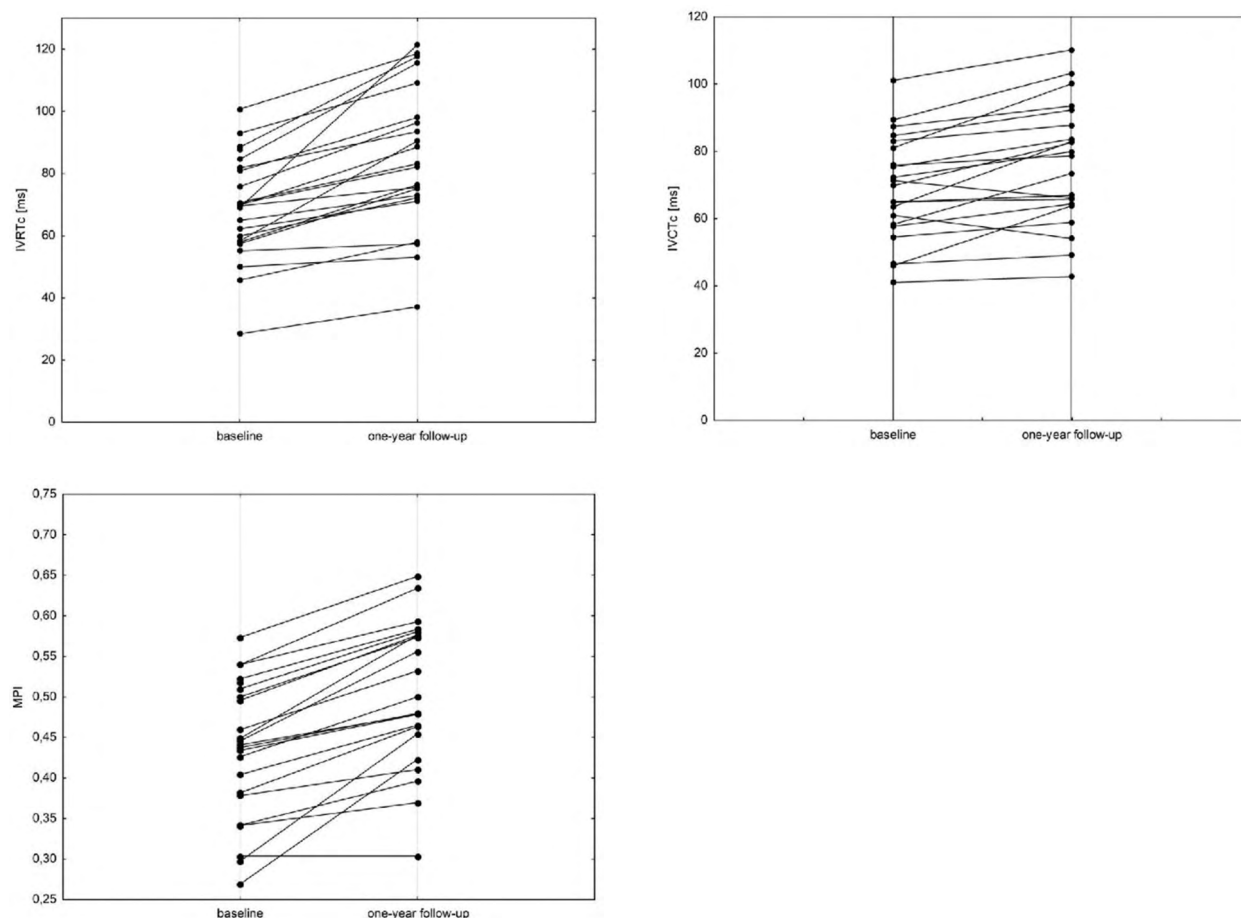


Figure 4. Isovolumic relaxation time (IVRT_c), isovolumic contraction time (IVCT_c) and myocardial performance index (MPI) corrected for heart rate at baseline and at one-year follow-up

did not differ significantly. However trend for a decrease in TAPSE and S' was noted suggesting a deterioration in RV longitudinal function. These results are inconsistent with the study of Tanasa et al. [6]. These authors, with the use of two-dimensional speckle tracking ECHO, revealed amelioration of RV function at 3, 6, and 12 months compared to the pre-HD values.

Despite the limitations of TAPSE and S' such as neglecting the contribution of RV radial shift and being influenced by overall heart motion, these parameters are easily reproducible, significantly related to right ventricular ejection fraction calculated (EF_{RV}) on CMR [14]. TAPSE has been shown to be related to RV FAC assessed by ECHO. FAC is a more comprehensive parameter, incorporating both the longitudinal and radial planes of RV, and is related to EF_{RV} assessed with CMR [14]. Moreover, significant relation between FAC, TAPSE, and S' with EF_{RV} assessed by three-dimensional speckle-tracking ECHO (3D STE) has been shown [15]. In patients with heart failure, TAPSE and FAC have proven prognostic value. Reduced S' at the beginning of HD was confirmed as a powerful predictor of mortality [16].

Our study showed interesting observations regarding cardiac time intervals. However, none of these parameters is recommended as a single marker of RV function or pulmonary artery pressure (PAP) due to their intrinsic limitations. At follow-up we have shown a significant increase in RV heart rate-adjusted IVRTc and IVCTc, increase in MPI and decrease in IVAc all of these suggesting impairment of RV function. Active myocardial relaxation plays an important role in RV filling pattern and prolonged IVRT is an early indicator of diastolic dysfunction. A linear relationship between IVRT and invasive measurements of systolic pulmonary artery pressure (sPAP) was described by Burstin and confirmed in multiple studies [17, 18]. MPI has an established prognostic value in pulmonary hypertension patients and correlates well with FAC [18], as well as with more advanced indices derived from CMR [19]. IVA is considered a reliable and load-independent measurement of RV contraction. It correlates with the severity of illness in conditions affecting right heart function, e.g., obstructive sleep apnea, mitral stenosis, pulmonary hypertension [20].

Initially, major attention has been focused on LV. A few studies assessing impact of HD implementation on LV function show conflicting results: deterioration of LV ejection fraction (EF_{LV}) in the CRIC study [21], worsening of LV diastolic function without changes in systolic function in the CASCADE study [22], no changes in EF_{LV} in the IDEAL study [23], while improvement of LV function was reported by Ganda et al. [24]. In our study, after one year period of

maintenance HD, we observed non-significant changes in LV dimensions and EF_{LV} , but a tendency towards worsening of LV diastolic function was noted, as reflected by a decrease in early diastolic mitral annular velocity and an increase in E/e'_{LV} ratio.

We have noted a non-significant decrease in plasma NT-proBNP at one-year follow-up since HD initiation. It might seem confusing considering the revealed in this study deterioration of RV function, along with the tendency for impairment of LV function and non-significant increase in sPAP. Concerning the fact that NT-proBNP is an established marker of hypervolemia in patients undergoing HD irrespective of LV ejection fraction [25] our results may suggest a crucial role of optimized fluid status in ESRD patients on maintenance HD. A decrease in RVOT dimensions goes along with this line of thinking.

RV function analysis is a dynamically developing branch of ECHO. TDI, STE and application of three-dimensional imaging expand the possibilities of assessment of the RV complex structure and function. However, these methods require images of excellent quality and are not yet widely available in clinical practice.

The most important limitation of this study is the small sample size. It is due to the problems with including patients in the study and with follow-up visits during the time of COVID19 pandemic and the Health Care Service reorganization. Moreover, the management of several factors involved in the development of cardiovascular abnormalities such as correction of hypertension and anaemia and adequacy of delivered dialysis dose were not analysed. The results may be also affected by the selection bias because of the high mortality rate in ESRD patients.

Long-term follow-up clinical studies with the use of different imaging modalities in a large number of patients are needed to disclose the impact of maintenance HD on cardiac structure and function.

Conclusion

In patients with ESRD a long-term HD negatively impacts RV function but the relation of this process with pulmonary pressure was not revealed. IVA and MPI measured with pulsed tissue Doppler are sensitive indicators of RV function.

Conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

Streszczenie

Wstęp. Wobec rosnącej liczby chorych wymagających leczenia nerkozastępczego oraz dwukierunkowych interakcji między nerkami a sercem, znanych jako zespół nerkowo-sercowy, ocena wpływu dializoterapii na funkcję serca stała się kluczowa.

Materiał i metody. Grupę badaną stanowiło 22 dorosłych pacjentów ze schyłkową niewydolnością nerek zakwalifikowanych do hemodializoterapii w Centrum Dializ między styczniem a grudniem 2019 roku.

Wyniki. Mediana wieku pacjentów wyniosła 59,5 roku (51–64). Kobiety stanowiły 55% badanej grupy. Najczęstszymi chorobami współistniejącymi były: nadciśnienie tętnicze (86%) oraz cukrzyca (36%). W obserwacji rocznej odnotowano istotny spadek wymiarów proksymalnego i dystalnego RVOT (odpowiednio: $p = 0,04$; $p = 0,007$) oraz istotny spadek wartości IVAc ($p = 0,01$). W konsekwencji wydłużenia IVRTc ($p < 0,001$) i IVCTc ($p < 0,001$) zaobserwowano istotny wzrost wartości MPI ($p < 0,001$).

Wnioski. U pacjentów ze schyłkową niewydolnością nerek długotrwała dializoterapia wpływa negatywnie na funkcję prawej komory. IVA oraz MPI, mierzone metodą tkankowego Dopplera pulsacyjnego, są czułymi wskaźnikami zmian w prawej komorze.

Słowa kluczowe: dializy, echokardiografia, funkcja prawej komory, schyłkowa niewydolność nerek

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