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Echocardiographic assessment of right ventricular functions in nondiabetic normotensive hemodialysis patients

YUSUF KARAVELIOĞLU[1], SULTAN ÖZKURT[2], MACİT KALÇIK[3,*], HEKIM KARAPINAR[4], ARIF ARISOY[5]

[1]Department of Cardiology, Corum Training and Research Hospital, Hitit University, Çorum, Turkey
[2]Department of Nephrology, Corum Training and Research Hospital, Hitit University, Çorum, Turkey
[3]Department of Cardiology, İskilip Atıf Hoca State Hospital, Çorum, Turkey
[4]Department of Cardiology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey
[5]Department of Cardiology, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey
*Corresponding author: Macit Kalçık, MD; İskilip Atıf Hoca State Hospital, Meydan Mah, Toprak Sok, No: 7/8 İskilip, Çorum, Turkey; Phone: (90)536 4921789; Fax: +903645113187; E-mail: macitkalcik@yahoo.com

Abstract: *Purpose:* Heart is affected structurally and functionally in end-stage renal disease (ESRD). However, the data available about adverse effects of ESRD on right ventricle (RV) is scarce. We aimed to evaluate echocardiographic parameters of RV in nondiabetic, normotensive patients with ESRD undergoing hemodialysis (HD). *Methods:* A total of 45 (24 women; mean age 52.4 ± 12.4 years) consecutive nondiabetic, normotensive patients with ESRD undergoing HD and 39 healthy age and sex-matched control subjects (22 women; mean age 50.3 ± 6.6 years) were enrolled in the study. M-mode and two dimensional images, color, pulsed and continuous wave Doppler, and tissue Doppler measurements were acquired from all subjects. Echocardiographic evaluation was performed in the days between HD dates of the patients. *Results:* RV fractional area change, tricuspid annular plane systolic excursion, tricuspid *E* velocity, *E/A* ratio, tricuspid annular *E′* velocity, and *E′/A′* ratio were lower in patients than controls ($p < 0.001$, $p = 0.003$, $p = 0.007$, $p = 0.005$, $p < 0.001$, and $p = 0.034$, respectively). However, RV diastolic area, RV myocardial performance index, *E/E′* ratio, and mean and systolic pulmonary artery pressure were higher in patients than controls ($p < 0.001$, $p = 0.007$, $p = 0.005$, $p < 0.001$, $p = 0.006$, respectively). *Conclusions:* RV systolic and diastolic functions of nondiabetic, normotensive HD patients are deteriorated as compared to healthy controls.

Keywords: hemodialysis, right ventricle, tissue Doppler echocardiography, myocardial performance index

Introduction

Significant increase in cardiovascular morbidity and mortality is reported in patients with end-stage renal disease (ESRD). Cardiovascular diseases are the most common cause of death in this group of patients [1]. Several studies showed that left ventricular systolic and diastolic functions were deteriorated in patients with chronic renal disease and this was associated with worse clinical outcomes [2]. Although the relationship between right ventricle (RV) dysfunction and adverse outcomes has been shown in many diseases and preclinical conditions [3], little is known about RV in nondiabetic, normotensive hemodialysis (HD) patients.

There are many difficulties in evaluation of RV due to peculiar anatomy and retrosternal localization [4]. RV functions may be appreciated with different techniques such as catheterization, nuclear magnetic resonance imaging, and echocardiography [5–7]. Different methods have been tried to overcome this technical difficulty in echocardiographic evaluation. Several echocardiographic parameters such as fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic velocities, and myocardial performance index (MPI) derived by tissue Doppler imaging have been well described in the evaluation of systolic and diastolic functions of RV [8, 9].

Hypertension (HT) and diabetes mellitus (DM) are frequently accompanying disorders in patients undergoing hemodialysis (HD) which may affect RV functions. We aimed to evaluate RV functions in terms of mentioned parameters in nondiabetic, normotensive patients with ESRD undergoing HD.

Materials and Methods

Population and study protocol

This was a cross-sectional, observational prospective study, and a total of 45 (24 women, 21 men; mean age 52.4 ± 12.4 years) consecutive nondiabetic, normotensive HD patients were recruited. Subjects were selected from patients who had been routinely treated in the hemodialysis unit of Hitit University Corum Research and Training Hospital for at least 1 year and received standardized HD prescriptions (500 mL/min dialysate flow; 200–250 mL/min blood flow; 4 h of dialysis per session; 3 sessions per week). Exclusion criteria were HT (history of hypertension or office blood pressure ≥140/90 mmHg or being on antihypertensive medication), DM (fasting blood glucose > 125 mg/dL or HbA1$_C$ > 6.5% or being on antidiabetic medication), clinical and echocardiographic findings of systolic heart failure (LV ejection fraction [EF] less than 50%), and coronary artery disease (clinical or ECG evidences of myocardial ischemia, i.e., angina pectoris, segmental wall motion abnormalities on echocardiography, ischemic changes on ECG or known coronary artery disease). Patients without sinus rhythm, patients with moderate or severe valvular heart disease, pericardial disease, previous renal transplantation, and clinical signs of over hydration, and those who have inadequate echocardiographic imaging were also excluded from the study. The age- and gender-matched 39 healthy subjects (22 women, 17 men; mean age 50.3 ± 6.6 years) were enrolled as the control group. The study was approved by the local ethics board. Examinations of the patients confirmed to good medical and laboratory practices and recommendations of the Declaration of Helsinki on Biomedical Research Involving Human Subjects. Informed consent was taken from all participants.

The physical examination of all patients was undertaken on a day that they were not receiving HD therapy. Blood samples were obtained in the morning after an overnight fasting (before starting a dialysis session in HD patients). Blood pressure (BP), heart rate, demographic characteristics, clinical history, laboratory parameters, and medications of the patients were recorded. Routine serum biochemical variables including glucose, calcium, phosphorus, hemoglobin, albumin, and lipids were analyzed using standard laboratory methods. Serum PTH levels were measured by immunoradiometric assay.

Echocardiography

Echocardiographic examinations were performed with 2–4 MHz phased array transducer attached to a Vivid S5 echocardiography machine (GE, Horten, Norway) by a cardiologist who was blinded to clinical details of each subjects. Single lead ECG was recorded continuously during the echocardiographic examination in left lateral decubitus position during end-expiratory apnea. M-mode and two dimensional images, color, and pulsed and continuous wave Doppler measurements were acquired from all subjects compatible with standard echocardiographic application methods. Left ventricular EF of all subjects were calculated by using biplane Simpson's method.

Inferior vena cava (IVC) diameter and collapse, and E/E' ratio were measured to evaluate the preload; systolic and mean pulmonary arterial pressure (PAP) were measured to evaluate the afterload; FAC, S' velocity, TAPSE, and TDI-derived MPI were measured to evaluate systolic function; tricuspid E wave velocity, E/A ratio, E' velocity, and E'/A' ratio were measured to evaluate diastolic function of RV.

Systolic PAP was estimated by adding estimated right atrium (RA) pressure to the tricuspid regurgitation (TR) jet velocity, if present (4 × TR velocity^2 + RA pressure). Inferior vena cava diameter at end-expiration and its respiratory collapse were recorded. Mean PAP was calculated by using pulmonary acceleration time (AT) measured by pulsed Doppler of the pulmonary artery in systole with the formula "Mean PAP = 79 – (0.45 × AT)" [10]. The formula "Mean PAP = 90 – (0.62 × AT)" was used in patients with AT < 120 ms [11].

TAPSE was calculated by placing an M-mode cursor through the tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole in the standard apical 4-chamber view.

FAC was obtained by tracing the RV endocardium both in end-systole and end-diastole from the annulus, along with the free wall to the apex, and then back to the annulus along with the interventricular septum in the standard apical 4-chamber view. Right ventricular FAC was calculated using the formula FAC = (end-diastolic area – end-systolic area) / end-diastolic area × 100 [12].

Pulsed wave TDI (tissue Doppler image) was obtained by activating the machine's tissue Doppler imaging function with gains adjusted to eliminate transvalvular flow velocities and minimize noise. In the *apical 4-chamber view,* a 5–10 mm sample volume was placed at the lateral side of the tricuspid annulus. Measurements were recorded during the end-expiratory apnea in order to minimize the respiratory effect.

On the TDI images, annular peak systolic velocity (S), early (E') and late (A') peak annular diastolic velocities, and systolic velocity duration were measured as ejection time (ET), isovolumetric relaxation time (IVRT, time between the end of ET and the beginning of E'), and

isovolumetric contraction time (IVCT, time between the end of A′ and the beginning of ET) were measured. The final values of all parameters were recorded as the average of measurements of three cardiac cycles. Tricuspid valve closure and opening time (TCO) which was measured from the cessation of the A′ wave to the beginning of the E′ wave, encompassed IVCT, ET, and IVRT. The TDI-derived MPI, as a global estimate of both systolic and diastolic functions of the RV, was calculated as the sum of IVCT and IVRT divided by the ET with the formula "TDI-MPI = (TCO-ET) / ET" [4].

Intra-observer variability was assessed in 20 patients by repeating the measurements on two occasions under the same basal conditions. In order to evaluate the inter-observer variability, the measurements were recorded offline from digital recordings by a second observer who was blinded to the results of the first examination.

Statistical analysis

Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Continuous variables were presented as mean ± standard deviation and compared by Student t-test if normally distributed or presented as median (25th–75th percentiles) and compared by Mann–Whitney U test if not compatible with normal distribution. Categorical variables were summarized as percentages and compared with the Chi-square test. Pearson test was used in correlation analysis between parametric variables. Spearman's ρ test was used in the correlation analysis of nonparametric variable. A two-sided p value <0.05 was considered as statistically significant.

Results

The indications for HD in the patient group were polycystic kidney disease in 13 (28.8%), pyelonephritis in 7 (15.6%), glomerulonephritis in 9 (20%), hydronephrosis in 10 (22.2%) toxic nephropathy in 4 (8.9%), and unknown in 2 (4.5%) patients. All patients had radial arteriovenous fistula.

Groups were similar in terms of age and gender [52.4 ± 12.4 vs. 50.3 ± 6.6 years, p = 0.347; 21 (47%) vs.

Table I Demographic characteristics and laboratory results of the groups

	ESRD patients (n = 45)	Controls (n = 39)	p value
Age (years)	52.4 ± 12.4	50.3 ± 6.6	0.347
Male, n (%)	21 (47)	17 (44)	0.779
Body surface area (m²)	1.67 ± 0.2	1.82 ± 0.15	<0.001
Body mass index (kg/m²)	26.4 ± 6.2	28.5 ± 3.9	0.069
Resting heart rate (beats/min)	74.9 ± 9.9	65.8 ± 7.9	<0.001
Systolic BP (mmHg)	113.1 ± 19.3	115.0 ± 8.8	0.585
Diastolic BP (mmHg)	70.9 ± 10.5	74.4 ± 6.7	0.078
HD duration (months)	84 (60–141)	–	–
Urea (mg/dL)	150 ± 32	30 ± 7	<0.001
Creatinine (mg/dL)	9.8 ± 2.4	0.8 ± 0.2	<0.001
Glucose (mg/dL)	86.3 ± 15.4	95.1 ± 7.4	0.001
Potassium (mEq/L)	5.5 ± 0.6	4.4 ± 0.3	<0.001
Calcium (mg/dL)	8.8 ± 0.9	9.5 ± 0.4	<0.001
Phosphorus (mg/dL)	5.2 ± 1.1	3.6 ± 0.5	<0.001
Parathyroid hormone (pg/mL)	503 ± 405	54 ± 20	<0.001
Albumin (g/dL)	3.9 ± 0.3	4.7 ± 0.3	<0.001
Uric acid (mg/dL)	6.9 ± 1.2	4.8 ± 0.9	<0.001
Total cholesterol (mg/dL)	181 ± 40	206 ± 49	0.016
Triglycerides (mg/dL)	193 ± 73	149 ± 101	0.030
Hemoglobin (g/dL)	11.7 ± 1.1	13.9 ± 1.6	<0.001
Hematocrit (%)	34.3 ± 3.0	42.6 ± 4.4	<0.001

BP: blood pressure, ESRD: end-stage renal disease, HD: hemodialysis

Table II ┃ Echocardiographic characteristics of groups

	ESRD patients (*n* = 45)	Controls (*n* = 39)	*p* value
Left heart values			
LVEDD (mm)	47.3 ± 4.9	47.6 ± 5.9	0.328
LVEDD index (mm/m^2)	28.8 ± 4.5	26.3 ± 3.2	0.004
LV ejection fraction (%)	66.0 ± 5.7	67.5 ± 4.4	0.174
LV mass index g/m^2	110.7 ± 30.3	84.3 ± 24.9	<0.001
Left atrial diameter (mm)	34.1 ± 5.1	31.9 ± 4.4	0.044
Left atrial diameter index mm/m^2	20.7 ± 3.7	17.7 ± 2.5	<0.001
Right heart values			
RV diastolic area (cm^2)	15.7 ± 2.3	12.4 ± 3.1	<0.001
RV diastolic area index (cm^2/m^2)	8.8 ± 1.6	7.6 ± 2.1	0.010
RV fractional area change (%)	40.1 ± 7.7	48.4 ± 9.9	<0.001
IVC diameter (mm)	13.1 ± 7.4	10.9 ± 6.0	0.282
Inspiratory IVC collapse (%)	42.6 ± 12.9	78.9 ± 12.9	<0.001
More than mild TR, *n* (%)	21 (47)	3 (8)	<0.001
Mean PAP (mmHg)	25.6 ± 6.9	15.3 ± 4.6	<0.001
Systolic PAP (mmHg)	41.9 ± 12.7	24.5 ± 3.8	0.006
E (cm/s)	49.9 ± 9.5	55.7 ± 9.5	0.007
E/A ratio	1.07 ± 0.48	1.38 ± 0.19	0.005
S (cm/s)	11.8 ± 3.1	12.8 ± 2.9	0.135
E′ (cm/s)	8.4 ± 3.5	12.0 ± 3.3	<0.001
A′ (cm/s)	15.0 ± 4.2	14.1 ± 4.6	0.336
E′/A′ ratio	0.59 ± 0.29	1.19 ± 1.67	0.034
E/E′ ratio	7.6 ± 4.0	5.0 ± 1.4	0.005
TDI-derived MPI	0.63 ± 0.23	0.51 ± 0.17	0.007
TAPSE (mm)	2.32 ± 0.42	2.56 ± 0.29	0.003

ESRD: end-stage renal disease, IVC: inferior vena cava, LVEDD: left ventricular end-diastolic diameter, LV: left ventricle, RV: right ventricle, TR: tricuspid regurgitation, PAP: pulmonary artery pressure, TDI: tissue Doppler imaging, MPI: myocardial performance index, TAPSE: tricuspid annular plane systolic excurtion

17 (44%) male, *p* = 0.779]. Furthermore, there was no significant difference between the patients and controls with respect to systolic and diastolic BP (113.1 ± 19.3 vs. 115.0 ± 8.8 mm Hg, *p* = 0.585, and 70.9 ± 10.5 vs. 74.4 ± 6.7, *p* = 0.078, respectively), but heart rate was higher in the ESRD group (74.9 ± 9.9 vs. 65.8 ± 7.9 beats/min, *p* < 0.001). Body mass indices (BMI) of groups were similar (26.4 ± 6.2 vs. 28.5 ± 3.9 kg/m^2, *p* = 0.069), whereas mean body surface area (BSA) of the control group was significantly higher than that of the patients (1.82 ± 0.15 vs. 1.67 ± 0.2 m^2, *p* < 0.001). The ESRD patients had been on hemodialysis program for a median of 84 (60–141) months. Mean weight change at the end of each dialysis sessions was 2.69 ± 1.02 kg. In the laboratory test, triglyceride, uric acid, urea, creatinine, potassium, phosphorus, and parathyroid hormone (PTH) levels were significantly higher; however, glucose,

calcium, albumin, total cholesterol, hemoglobin, and hematocrit levels were found to be significantly lower in the ESRD patients. Demographic characteristics and laboratory results of the groups were presented in *Table I*.

There was no significant difference between groups with respect to LV end-diastolic dimension, and LV ejection fraction; however, LV end-diastolic dimension index, left atrial (LA) diameter, LA diameter index, and LV mass index were higher in the ESRD group. VCI diameters of groups were similar, but inspiratory collapse was less, and *E/E′* ratio was higher in ESRD patients than controls. RV diastolic area, RV diastolic area index, frequency of tricuspid regurgitation, and mean and systolic PAP values were higher in ESRD patients than that of controls *(Table II)*. Tricuspid *S* velocity was similar between groups, while FAC *(Fig. 1)* and TAPSE *(Fig. 2)* were lower (40.1 ± 7.7 vs. 48.4 ± 9.9%, *p* < 0.001, and
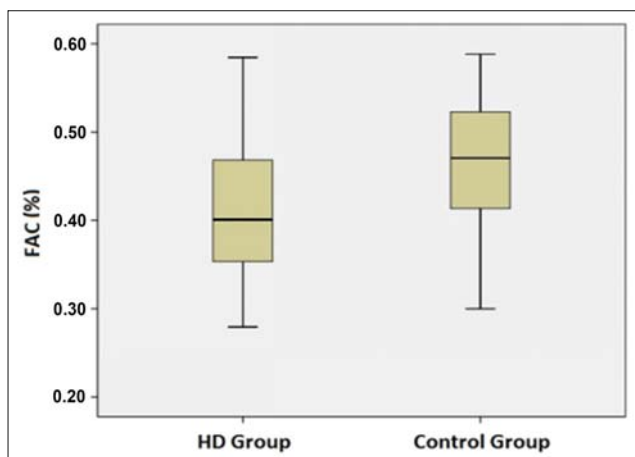
Fig. 1. The box-plot graph comprising of fractional area change values between hemodialysis patients and control subjects *Abbreviations:* HD = hemodialysis, FAC = fractional area change
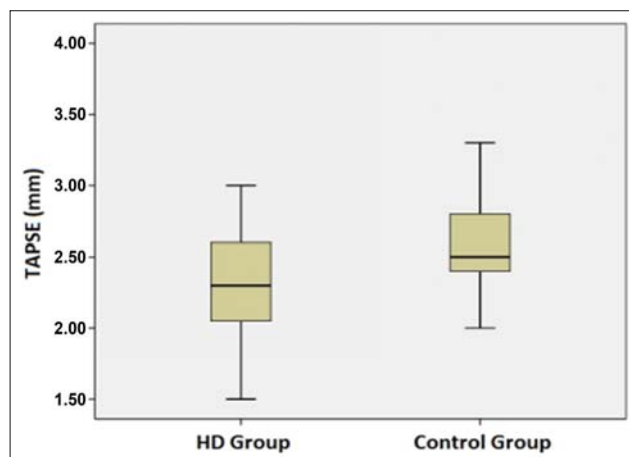

Fig. 2. The box-plot graph comprising of tricuspid annular plane systolic excursion values between hemodialysis patients and control subjects. *Abbreviations:* HD = hemodialysis, TAPSE = tricuspid annular plane systolic excursion
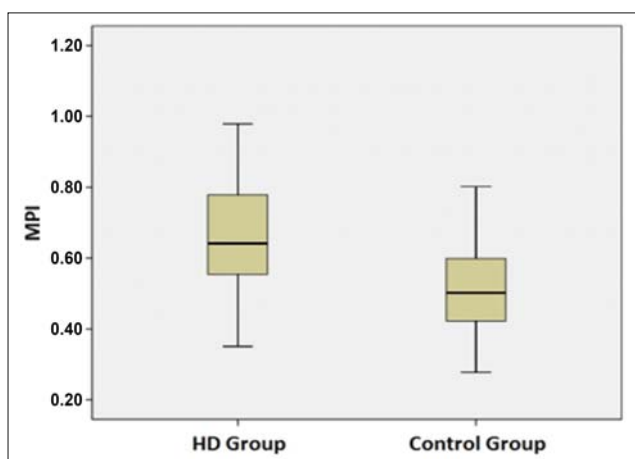

Fig. 3. The box-plot graph comprising of right ventricle myocardial performance index values between hemodialysis patients and control subjects. *Abbreviations:* HD = hemodialysis, MPI = myocardial performance index

2.32 ± 0.42 vs. 2.56 ± 0.29 cm, $p = 0.003$, respectively), and MPI *(Fig. 3)* was higher (0.63 ± 0.23 vs. 0.51 ± 0.17 $p = 0.007$) in ESRD group reflecting diminished RV systolic functions. In respect to RV diastolic functions, tricuspid E velocity and E/A ratio, tricuspid annular E' velocity, and E'/A' ratio were significantly lower in the ESRD group ($p = 0.007$, $p = 0.005$, $p < 0.001$, $p = 0.034$, respectively). A' velocity was similar in both groups. The results of the echocardiographic measurements are presented in *Table II*.

Discussion

This study revealed that preload and afterload of right ventricle increased, while FAC, TAPSE, and MPI, which are indicators of right ventricular systolic functions, and

the parameters associated with diastolic functions were deteriorated in patients with ESRD undergoing HD as compared to healthy subjects.

Possible causes of right ventricular changes in patients undergoing HD may be uremia, fluid retention, renal anemia, hyperparathyroidism, and high AV shunt flow [13–15]. Although RV works against low pressure in normal situations, it can adapt to high volume changes. However, this contractile reserve is limited, and in patients, with chronic renal failure in whom high volume changes occur, RV dysfunction may develop after a while. Transthoracic echocardiography is the most commonly used diagnostic tool for the evaluation of RV functions in clinical practice. However, there are some difficulties in the evaluation of RV because its functions are closely related with many variables like preload, heart rate, and age.

Since HT, DM, coronary artery disease, and heart failure are frequently seen in patients undergoing hemodialysis, diastolic dysfunction frequently accompanies to ESRD in this group of patients [16–18]. It was shown that RV function is adversely affected in the presence of HT [19] and DM [20]. Therefore, in our study, we excluded the patients with HT and DM in order to get rid of their effects on RV functions.

Since diastolic parameters of RV are affected from abrupt volume changes during dialysis, it has been investigated in many studies, and there is conflicting data regarding this issue. Arinc et al. showed that RV systolic and diastolic velocities detected by TDI were not or only minimally affected from preload reduction in hemodialysis patients [21]. Drighil et al. showed that both systolic and diastolic TDI velocities of the RV are preload dependent [22]. It is known that E/E' value is a relatively less volume dependent variable [23]. In the present study, in order to minimize these changes, we gathered data at the midday of two dialysis days of our patients, and this

is why we tried to purify our variables from conflicting affects of high or low volume load.

TAPSE, the annular motion of RV towards the apex, is generally used as a prognostic marker in several cardiac disorders. For example, low TAPSE values indicate poor prognosis in patients with idiopathic pulmonary arterial hypertension [24]. In addition, TAPSE was found to be well correlated with RV EF which was calculated by radionuclide angiography [25]. With the lowest intra- and inter-observer variability, TAPSE < 2 cm indicates that the RV EF is below 40% measured with RV fractional area change [26, 27]. Although TAPSE values increase from birth to adolescence, it does not change through adulthood [28, 29]. Also, we did not observe any correlation between TAPSE and age in this study. However, TAPSE does not give any information about segmental wall motion abnormalities. Also, reliability of TAPSE decreases in the presence of severe tricuspid regurgitation [30]. Thus, we did not include patients with severe TR in order to exclude the conflicting affect of tricuspid regurgitation on TAPSE values. Additionally, RV function might be affected by an impaired left ventricular function, so this group of patients was not included in the present study.

Supranormal TAPSE values are seen in patients with atrial septal defect, and it has been shown that this value diminishes to normal ranges after closure of the defect with devices [31]. In this manner, TAPSE value may be found higher in patients undergoing hemodialysis due to volume overload; however, we found that our ESRD patients undergoing HD had significantly lower TAPSE values compared to healthy controls.

The correlation between TAPSE and heart rate (HR) is thought to be linear and negative by some authors. A number of studies have shown that HR has a clear influence on tricuspid annular plane movement, while some others not [32]. In our study, there was no correlation between HR and TAPSE in both groups.

Reliability of RV EF values estimated by FAC is low because of the complex RV geometry and unclear surfaces of trabeculated endocardium [33]. Normal values for RV EF vary from 32% to 60% [34]. In our study, mean RV EF values were found within normal ranges in each group while ESRD patients had significantly lower RV EF values compared to controls. There are some difficulties in evaluation of echocardiographic parameters used to understand RV functions due to disadvantages in RV structural geometry. MPI, as a nongeometrical parameter, is calculated by using Doppler via division of the sum of IVCT and IVRT to the ET [35]. Similar to left ventricle, MPI can be calculated for RV, and it is a less affected parameter from HR [36], preload [37], and afterload. In our study, there was a statistically significant difference between patients and healthy controls in terms of MPI values, reflecting both RV systolic and diastolic functions.

IVC diameter and respiratory variation are important indicators of right atrial pressure. A diameter of less than 1.5 cm in long axis with normal respiratory variation (~50%) corresponds to right atrial pressures <10 mmHg [35]. In our study, we found that there was no significant difference between groups in terms of IVC diameters, whereas respiratory variation in IVC was significantly different. This may indicate a subclinical influence on RV functions.

Limitations

This was a cross-sectional study including relatively small number of ESRD patients without DM and HT. Subclinical pulmonary disease or venous thromboembolic conditions were not systematically excluded which may affect RV functions. Although echocardiographical parameters were measured on the day between HD days, volume changes may have influence on RV functions in patients undergoing hemodialysis.

Conclusions

This study shows that RV systolic and diastolic functions are disrupted in hemodialysis patients without HT and DM. Intrinsic pathophysiological processes occurring in chronic renal failure such as inflammation and fibrosis may lead to these results.

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Conflict of interest: The authors report no conflict of interest.

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