

## Echocardiographic Assessment of Right Ventricular Function in Normotensive Non Diabetic Hemodialysis Patients

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**Abstract:** *Background:* 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 normotensive, nondiabetic patients with ESRD undergoing hemodialysis (HD). *Methods* The study was conducted on 75 individuals classified into two groups: 50 patients with end stage renal disease on regular hemodialysis for more than one year (group one) and 25 persons of normal individuals as control group (group two). All patients and control were subjected to full medical history, full clinical examination and laboratory investigations including Serum creatinine, complete blood count (CBC), C-reactive protein (CRP), fasting blood glucose levels, lipid profile (triglycerides and cholesterol), Serum calcium (CA), phosphorus (PO4), and intact parathyroid hormone (IPTH). Also M-mode and two dimensional images, 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, 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 normotensive, nondiabetic HD patients are deteriorated as compared to healthy controls.

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### 1. Introduction:

Chronic kidney disease is a disorder of epidemic proportions that impairs cardiac function. (1) the understanding of new nontraditional predictors of mortality could improve their outcomes. Right ventricular systolic dysfunction (RVSD) has recently been recognized as a predictor of cardiovascular death in heart failure and hemodialysis patients. However, the factors contributing to RVSD in hemodialysis patients remain unknown. (1) Cardiovascular disease is the leading cause of mortality in patients undergoing dialysis. (1) Cardiac failure develops as many as 25 to 50% in hemodialysis patients (2). However, the systematic assessment of right heart function is not uniformly carried out. This is due partly to the enormous attention given to the evaluation of the left heart, a lack of familiarity with ultrasound techniques that can be used in imaging the right heart, and a paucity of ultrasound studies providing normal reference values of right heart size and function (3). Hemodialysis (HD) which is usually carried out via a surgically created native arteriovenous fistula (AVF) has been associated with an increased risk of

pulmonary hypertension (PH) (4), a condition reported as a predictor of mortality in these patients (5). The arteriovenous fistula causes a left to right shunt, leading to chronic volume overload and right ventricular function impairment. (1) Right ventricular systolic dysfunction has been shown to inversely correlate with glomerular filtration rate in chronic kidney disease patients and has been poorer in hemodialysis patients than in healthy controls (6). Hemodynamic derangement constitutes a substantial part of the overall cardiovascular risk in dialysis patients (7). This relates in part to the adverse effects of recurrent or chronic volume and pressure overload on the heart and the cardiovascular tree. In addition, hypertrophic or dilated cardiomyopathy is very common among patients at initiation of dialysis, which limits the capability of the cardiovascular system to cope with excess fluids, thus complicating optimal volume management in dialysis care (8) Echocardiography is an established method for the assessment of left ventricular and right ventricular function. Most conventional Echocardiographic parameters of LV and RV systolic and diastolic

function are known to be load dependent )9) A lot of prospective and retrospective experimental and clinical studies showed that measurement of tricuspid annular velocities using tissue Doppler imaging (TDI) is a simple and reliable method for the assessment of global systolic and diastolic RV function (10).

## 2. Patients and Methods:

Eighty four subjects will be included in this study and will be divided into two groups as follow:-

Group I:- includes ( 45 ) patients end stage renal disease (ESRD) on regular hemodialysis in Nephrology Unit, at Al-Hussein University Hospital not less than one year, they are (21) male and (24) female, and receive three hemodialysis sessions weekly, for four hours per each, using Fresenius machines 4008s, Bicarbonate dialysate containing (in millimoles per liter) 32 bicarbonate, 136–138 sodium, 2.5–4.0 potassium, 1.0 magnesium, and 1.25 or 1.5 calcium.

Group II:- includes (39) apparently healthy Subjects ((17) male and (22) female) matched with age and sex with ( group I) as a control group.

All subjects will be subjected to the following:

**A-**writing consent will be taken from all patients.

**B-** History taking and Clinical examination from every patient included In the study. Complete history taking including determination of duration of hemodialysis and its time of each session, type of dialysis machines, type of filter, any risk factors for any type of cardiac disease or past history of myocardial infarction, History of previous kidney transplantation, hypertension, diabetes and ischemic heart disease.

**C-**Laboratory Investigations to evaluate: Serum creatinine, hemoglobin %, C-reactive protein (CRP), fasting blood glucose levels., lipid profile, Serum calcium (CA), phosphorus (PO<sub>4</sub>), and intact parathyroid hormone (IPTH).

**D-** Transthoracic echocardiographic examination: A Philips IE 33 phased array system equipped with TDI technology was used. All the patients will be examined in the left lateral decubitus position. Echocardiographic images were acquired from the standard views (left parasternal long-axis (PLAX), apical four –chamber, modified apical 4-chamber, parasternal short-axis (PSAX), left parasternal RV inflow, right ventricle–focused apical 4-chamber and subcostal views). recordings and different measurements were obtained according to the American society of Echocardiography guidelines (11), (12).

• The following measurements will be taken:

1) Left ventricular end-diastolic diameter (LVEDd) for male (42-58.4 mm) and for female (37.8-52.2mm).

2) left ventricular Ejection Fraction (EF): The normal value of EF is (52-72 %) for male and (54-74 %) for female

3) Left Ventricular Mass Index (LV mass / BSA): normal value for male (50-102) and for female (44-88) g/m<sup>2</sup>

4) Left Atrial diameter (LAD): Normal values for male (3-4cm) and for female (2.7-3.8cm).

• Assessment of the right side of the heart:

1) Measurement of the right ventricular area and calculation of the fractional area change (RVFAC):

Normal values of RVFAC: 35-63%.

2) Right ventricular End Diastolic Area (RVEDA): Normal values =10-25 cm<sup>2</sup>.

3) Measurement of the tricuspid Annular plane systolic excursion (TAPSE): Normal values of TAPSE: (1.7 – 3.1 cm).

4) The Inferior Vena Cava: ( Normal values <2.1 cm).

5) Systolic pulmonary artery pressure SPAP (15-30).

6) Diastolic Pulmonary Artery Pressure: (8-15).

7) Mean Pulmonary Artery Pressure: (9-18).

8) Systolic excursion velocity at lateral tricuspid annulus (S wave): Normal values: Peak systolic velocity at lateral tricuspid annulus (9.5-18.7 cm/sec).

9) Measurement of Myocardial Performance Index (MPI) or (Tei index): Using Tissue Doppler Method:

Normal values by tissue doppler (.22-.54).

10) Pulsed-wave Doppler: The following parameters were evaluated: peak tricuspid flow velocity in early diastole (E ) normal values (35-73 cm/sec) peak tricuspid flow velocity in late diastole (A ) normal values (21-58 cm/sec), and E/A ratio normal values (.8-2).

11) Tissue Doppler imaging (TDI): Measurements were made of peak systolic (S) normal values (9.5-18.7cm/sec), peak early diastolic (E') normal values (7.8-20.2 cm/sec) and late peak diastolic myocardial velocities (A') normal values (7-20cm/sec), (E/E') ratio normal values (2-6), and (E'/A') ratio normal values (.52-1.84) at the tricuspid annulus. Measurements were averaged for three cardiac cycles.

### Statistical Analysis:

Data was analyzed by Microsoft Office 2010 (excel) and Statistical Package for Social Science (SPSS) version 16. Parametric data was expressed as mean ± SD and non parametric data was expressed as number and percentage of the total. Comparing the mean ± SD of 2 groups was done using the student's t test. Measuring the mutual correspondence between two values was done using the Spearman correlation coefficient. P value > 0.05 is considered non-significant, value < 0.05 is considered significant and value < 0.01 is considered highly significant.

### 3. Results:

Group one and group two were similar in terms of age and gender [ $52.4 \pm 12.4$  vs.  $50.3 \pm 6.6$  years,  $p = 0.347$ ; 21 (47%) vs. 17 (44%) male,  $p = 0.779$ ]. Furthermore, there was no significant difference between the patients and controls with respect to systolic and diastolic BP ( $113.1 \pm 19.3$  vs.  $115.0 \pm 8.8$  mm Hg,  $p = 0.585$ , and  $70.9 \pm 10.5$  vs.  $74.4 \pm 6.7$ ,  $p = 0.078$ , respectively), but heart rate was higher in the ESRD group ( $74.9 \pm 9.9$  vs.  $65.8 \pm 7.9$  beats/min,  $p < 0.001$ ). Body mass indices (BMI) of groups were similar ( $26.4 \pm 6.2$  vs.  $28.5 \pm 3.9$  kg/m<sup>2</sup>,  $p = 0.069$ ), whereas mean body surface area (BSA) of the control

group was significantly higher than that of the patients ( $1.82 \pm 0.15$  vs.  $1.67 \pm 0.2$  m<sup>2</sup>,  $p < 0.001$ ). 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  $2.69 \pm 1.02$  kg. In the laboratory test, triglyceride, creatinine, phosphorus, and parathyroid hormone (PTH) levels were significantly higher; however, fasting blood glucose, calcium, total cholesterol, hemoglobin, and levels were found to be significantly lower in the ESRD patients. Demographic characteristics and laboratory results of the groups were presented in Table I.

Table I Demographic characteristics and laboratory results of the groups

	ESRD patients (n-45)	Controls (n-39)	P value
Age (years)	$52 \pm 12.4$	$50.3 \pm 6.6$	0.347
Male, n (%)	21 (47)	17 (44)	0.779
Body surface area (m <sup>2</sup> )	$1.67 \pm 0.2$	$1.82 \pm 0.15$	>0.001
Body mass index (kg/m <sup>2</sup> )	$26.4 \pm 6.2$	$28.5 \pm 3.9$	0.069
Heart rate (beats/min)	$74.9 \pm 9.9$	$65.8 \pm 7.9$	>0.001
Systolic BP (mmHg)	$113.1 \pm 19.3$	$115.0 \pm 8.8$	0.585
Diastolic BP (mmHg)	$70.9 \pm 10.5$	$74.4 \pm 6.7$	0.078
HD duration (months)	84 (60-141)		
Creatinine (mg/dl)	$9.8 \pm 2.4$	$0.8 \pm 0.2$	>0.001
Glucose (mg/dl)	$86.3 \pm 15.4$	$95.1 \pm 7.4$	0.001
Phosphorus (mg/dl)	$5.2 \pm 1.1$	$3.6 \pm 0.5$	>0.001
Calcium (mg/dL)	$8.8 \pm 0.9$	$9.5 \pm 0.4$	>0.001
Parathyroid hormone (pg/mL)	504 ± 405	54 ± 20	>0.001
Total cholesterol (mg/dL)	$181 \pm 40$	$206 \pm 49$	0.016
Triglycerides (mg/dL)	$193 \pm 73$	$149 \pm 101$	0.030
Hemoglobin (g/dL)	$11.7 \pm 1.1$	$13.9 \pm 1.6$	>0.001

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

There was no significant difference between groups with respect to LV end-diastolic dimension, and LV ejection fraction; however, left atrial (LA) diameter, was higher in the ESRD group. IVC diameters of groups were similar, and E/E<sup>1</sup> ratio was higher in ESRD patients than controls. RV diastolic area, 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 and TAPSE were lower ( $40.1 \pm 7.7$  vs.  $48.4 \pm 9.9$  %,  $p < 0.001$ , and  $2.32 \pm 0.42$  vs.  $2.56 \pm 0.29$  cm,  $p = 0.003$ , respectively), and MPI was higher ( $0.63 \pm 0.23$  vs.  $0.51 \pm 0.17$   $p = 0.007$ ) 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<sup>1</sup> 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.

### 4. Discussion:

This study revealed that preload and after load 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 HTN, 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 HTN 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.

Table II Echocardiographic characteristics of the groups

	ESRD patients (n-45)	Controls (n-39)	P value
<b>Left heart parameters</b>			
LVEDD (mm)	47.3 ± 4.9	47.6 ± 5.9	0.328
LV ejection fraction (%)	66.0 ± 5.7	67.5 ± 4.4	0.174
LV mass indexg/m <sup>2</sup>	110.7 ± 30.3	84.3 ± 24.9	>0.001
Left atrial diameter (mm)	34.1 ± 5.1	31.9 ± 4.4	0.044
<b>Right heart parameters</b>			
RV diastolic area (cm <sup>2</sup> )	15.7 ± 2.3	12.4 ± 3.1	>0.001
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 (cm)	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 excursion

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 after load. 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.

### Conclusion:

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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