DOI: 10.1111/j.1540-8175.2012.01749.x

Echocardiography

Ventricular Function in Patients with End-Stage Renal Disease Starting Dialysis Therapy: A Tissue Doppler Imaging Study

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Background: Heart failure is prevalent in end-stage renal disease (ESRD) patients on long-term dialysis. Detection of right ventricular (RV) dysfunction before starting dialysis may help to identify patients at a higher risk of developing heart failure. Aim: To assess RV function in predialysis patients using tissue Doppler imaging (TDI) derived myocardial performance index of RV (MPI-RV). Methods: Echocardiography including pulsed TDI of lateral tricuspid annulus was performed in 41 patients with ESRD before starting dialysis therapy and 12 age and gender matched healthy controls. RV dysfunction was defined as MPI > 0.4; a value above the median MPI in controls. Results: Compared to controls, ESRD patients had significantly higher blood pressure and lower hemoglobin level. MPI-RV was significantly impaired in ESRD patients compared to control (0.6 vs. 0.4, $P < 0.001$). RV dysfunction was identified in 23 ESRD patients (56%). ESRD patients had significantly lower e' velocity and e'/a' ratio as compared with controls. Pulmonary hypertension was detected in 15 (36.5%) patients. Among ESRD patients, no correlation was detected between MPI-RV and calculated mean pulmonary artery pressure ($r = –0.13$, $P = 0.47$), pulmonary artery systolic pressure ($r = –0.12$, $P = 0.6$), left ventricular ejection fraction ($r = 0.294$, $P = 0.06$), or MPI of left ventricle ($r = 0.3$, $P = 0.065$). ESRD patients with and without pulmonary hypertension had similar MPI-RV (0.6 vs.0.62, $P = 0.32$). Conclusion: Subclinical RV dysfunction—as estimated by TDI derived MPI—is highly prevalent among ESRD patients even before starting dialysis therapy. Pulmonary hypertension is not significantly associated with RV dysfunction in these patients. (Echocardiography 2012;29:1054-1059)

Key words: end-stage renal disease, myocardial performance index, right ventricle, tissue Doppler imaging

Background:

Congestive heart failure is prevalent in end-stage renal disease (ESRD) and is a leading cause of death in such patients.[1] While most available studies focused their attention on left ventricular (LV) dysfunction in ESRD patients, little attention has been directed towards right ventricular (RV) dysfunction. This is important since RV dysfunction has been associated with increased morbidity and mortality in many cardiovascular diseases.[2,3] In a recent study, RV dysfunction was reported in two-thirds of patients on long-term dialysis;[4] however, no data exists regarding the problem of RV dysfunction in ESRD patients before starting dialysis therapy. This may be important since detection of subclinical RV dysfunction in predialysis ESRD patients may help to identify patients at a higher risk of developing heart failure.

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Assessment of RV function by tissue Doppler imaging (TDI) is an accurate and reproducible method to detect preclinical ventricular abnormalities and has been considered as a reliable predictor of prognosis.[5,6] Accordingly, this study was designed to investigate RV function in predialysis ESRD patients using TDI.

Patients and Methods:

This was a prospective study conducted in Kasr Eini hospital, Cairo University in the interval between May 2009 and October 2010. The study population included 41 patients with ESRD scheduled for hemodialysis for the first time and 12 age and gender matched healthy controls. A written informed consent was obtained from all eligible patients. The research protocol was approved by the institute's committee on human research.

The following features were considered as exclusion criteria: age younger 15 years or older than 65 years; coronary artery disease (defined as the presence of one of the following: typical angina, pathological Q-waves or ST-segment or

T-wave changes specific for myocardial ischemia on ECG, a noninvasive stress test revealing ischemia or any perfusion abnormality, and history of a myocardial infarction or coronary revascularization); LV ejection fraction (LVEF) <40%; valvular lesions beyond mild severity using different quantitative and qualitative parameters based on American Society of Echocardiography (ASE) recommendations[7,8]; atrial fibrillation or paced rhythm; pericardial effusion with evident cardiac compression by echocardiography; constrictive pericarditis; haemoglobin level less than 8 gm/dL; or patients with advanced chronic obstructive pulmonary disease, interstitial pneumopathy, or chronic thromboembolic disease.

All patients were evaluated by clinical assessment, chest x-ray, laboratory tests, and comprehensive echocardiographic examination. Estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease equation.[9]

Echocardiographic Examination:

Images were obtained via Philips iE33 (Philips Medical Systems, Andover, MA, USA) with 2 and 2.5 MHz sector transducer equipped with TDI mode while the patient in the left lateral decubitus position. All measurements were taken on three consecutive beats and the mean values were used. No measurements were taken within five cycles of an ectopic beat.

LV diameters and wall thickness were measured according to criteria provided by the ASE.[10] LVEF was calculated using Simpson's rule. Three RV dimensions were taken in the apical four chamber view at end diastole:[10] basal RV measurement (RVD_1) at the level of tricuspid annulus; mid RV measurement (RVD_2) at the level of RV papillary muscles; and base-to-apex measurement (RVD_3).

Pulmonary artery systolic pressure (PASP) was calculated as: $4 \times$ (peak tricuspid regurge velocity)^2 + right atrial pressure.[11] Right atrial pressure was estimated from the diameter and respiratory motion of inferior vena cava in the subcostal view.[12] Pulmonary hypertension was defined as a value of PASP > 35 mmHg. Mean pulmonary artery pressure (MPAP) in mm Hg was calculated according to the equation: MPAP = 80 – (RV outflow acceleration time/2).[13,14] RV outflow tract acceleration time was measured as the time interval between the beginning of the pulmonary flow and its peak velocity with the pulsed-wave Doppler sample volume positioned in the region of the pulmonary valve annulus.

TDI:

In the apical four chamber view, the sample volume was placed at the lateral margin of the tricuspid annulus and the cursor was oriented so that it was parallel to the direction of the annulus motion. Wall filter was set at 100 Hz and the gain control was reduced to magnify the quality of the graphic signal. All velocities were measured, whenever possible, during end expiration. Peak systolic (s'), early diastolic (e'), and late diastolic (a') annular velocities were measured and e'/a' ratio was computed. Myocardial performance index (MPI) of RV was calculated by measuring two time intervals in the same cardiac cycle. A interval which represents the time interval between cessation of a'-wave and onset of the next e'-wave, and B interval which is the duration of s'-wave. MPI was calculated as (A – B)/B.[15] Similarly, MPI of LV was calculated by pulsed TDI analysis of lateral margin of the mitral annulus. Because of the lack of validation studies to define the upper normal reference of MPI-RV in different age groups and ethnic populations, RV dysfunction in this study was defined as MPI-RV value more than median value of MPI in the control group (MPI > 0.4).

Statistical Analysis:

Statistical analysis was performed using Statistical Package for Social Sciences, version 16 (SPSS 16). Using Kolmogrov–Smirnov test, all continuous variables showed abnormal distribution. Qualitative data were presented as number (percentage) while quantitative data were presented as median (range). Comparisons were performed using Mann–Whitney test and χ^2 analysis. Bivariate correlation was performed using Spearman correlation coefficient. Probability value of <0.05 was considered statistically significant.

Results:

Clinical Characteristics:

The baseline clinical characteristics of the study groups are shown in Table I. Both study groups were similar regarding age, gender, body mass index, and heart rate. Hemoglobin level was significantly lower in ESRD patients. Systemic hypertension was highly prevalent among ESRD patients (83%) and in many patients it was not adequately controlled with the consequence that systolic and diastolic blood pressure readings were significantly higher when compared to controls. The median duration between diagnosis of ESRD and enrolment was 9 days (range 3–60 days)

Echocardiographic Assessment of LV:

Both study groups showed similar LV cavity dimensions but LV wall thickness was significantly greater in ESRD group (Table II). Regional myocardial wall motion abnormalities at rest were detected in two patients; both had normal coronary angiography. Despite similar LVEF in both

TABLE I

Clinical Characteristics in Study Groups

	ESRD Group (n = 41)	Control Group (n = 12)	P Value
Age (year)	48 (21–65)	44 (47–65)	0.184
Male gender (%)	25 (60)	6 (50)	0.52
SBP (mmHg)	160 (100–200)	125 (95–130)	<0.001
DBP (mmHg)	100 (70–160)	70 (65–85)	<0.001
Heart rate (beats/min)	87 (60–120)	85 (58–94)	0.3
Hypertension (%)	34 (83)	–	
Diabetes mellitus (%)	7 (17)	–	
BMI (kg/m^2)	24.3 (19–19.2)	25.2 (20–30.1)	0.8
eGFR (mL/min)	10.2 (5.5–18)	114 (95–180)	<0.001
Serum creatinine (mg/dL)	8.5 (4.5–13.5)	0.8 (0.4–1.1)	<0.001
Hemoglobin (g/dL)	9 (8.2–13)	11.9 (10.9–15.3)	<0.001
Current medications (%)			
ACE-I/ARBs	9 (22)	–	
Beta-blockers	5 (12)	–	
Calcium channel blockers	9 (22)	–	
Statins	7 (17)	–	
Diuretics	16 (39)	–	

Data are presented as median (range), or number (%). ACE-I = angiotensin converting enzyme inhibitor, ARBs = angiotensin receptor blockers, BMI = body mass index, DBP = diastolic blood pressure, SBP = systolic blood pressure.

TABLE II

Echocardiographic Features of LV in Study Groups

	ESRD Group (n = 41)	Control Group (n = 12)	P Value
EDD (cm)	5.1 (4.0–7.2)	5.0 (4.5–5.5)	0.7
ESD (cm)	3.2 (2.3–5.8)	3.0 (2.3–3.4)	0.34
SWT (cm)	1.1 (0.7–1.7)	1.0 (0.8–1.1)	0.01
PWT (cm)	1.1 (0.8–1.8)	0.95 (0.8–1.1)	0.009
LV EF (%)	65 (43–75)	66 (60–69)	0.25
MPI-LV	0.7 (0.3–1.4)	0.45 (0.37–0.65)	0.002

Data presented as median (range). EDD = end diastolic dimension, ESD = end systolic dimension, PWT = posterior wall thickness, SWT = septal wall thickness.

study groups, MPI-LV was significantly higher in ESRD group indicating impairment in LV function in ESRD patients.

Echocardiographic Assessment of RV:

Echocardiographic features of RV in both study groups are summarized in Table III. MPI-RV was significantly higher in ESRD patients compared with controls suggesting an impairment of RV function in ESRD patients. When considering MPI-RV > 0.4 a threshold to define RV dysfunction, RV dysfunction was identified in 23 ESRD patients (56%). Of note, 18 patients (44%) exhibited MPI-RV > 0.55.

Among ESRD patients, no correlation was detected between MPI-RV and MPAP (r = –0.13, P = 0.47), PASP (r = –0.12, P = 0.6), LVEF (r = 0.294, P = 0.06), or MPI-LV (r = 0.3, P = 0.065). Diastolic function of RV was significantly impaired among ESRD patients as evident by the significant lower e' velocity and e'/a' ratio as compared with controls. Estimated MPAP significantly correlated with e'/a' ratio (r = –0.38, P = 0.013).

ESRD patients had higher calculated MPAP compared with controls. Pulmonary hypertension was detected in 15 (36.5%) ESRD patients versus none in controls (P = 0.012). No significant differences were detected between ESRD patients with and without pulmonary hypertension in terms of MPI-RV (0.6 vs. 0.62, P = 0.32) or s' velocity (13.5 cm/sec vs. 13.1 cm/sec, P = 0.89).

Discussion:

Knowledge about RV function in patients with ESRD has lagged extensively behind that of the LV. To the best of our knowledge no data exists regarding RV in ESRD patients starting dialysis therapy. This is important since a substantial number of ESRD patients on hemodilaysis have pulmonary hypertension and development or worsening of RV dysfunction in these patients is

TABLE III

Echocardiographic Features of RV in Study Groups

	ESRD Group (n = 41)	Control Group (n = 12)	P Value
RVD_1 (cm)	2.3 (1.98–2.7)	2.0 (1.8–2.4)	0.4
RVD_2 (cm)	2.2 (1.5–4.2)	2.4 (2.1–3.4)	0.496
RVD_3 (cm)	6.9 (4.5–9.6)	6.4 (4.5–7.3)	0.2
MPAP (mmHg)	27.5 (20–44)	20.5 (13–28.8)	0.049
Tricuspid TDI			
s′-wave (cm/sec)	13.4 (5.5–24)	13.8 (11–15)	0.59
e′-wave (cm/sec)	10.9 (6.0–19.5)	13 (8.1–18)	0.03
a′-wave (cm/sec)	18.5 (8.6–28)	15.2 (10–22)	0.12
e′/a′	0.57 (0.34–1.5)	0.84 (0.75–1.2)	0.001
MPI-RV	0.6 (0.27–1.2)	0.4 (0.28–0.5)	<0.001

Data presented as median (range).

associated with increased morbidity and mortality.[16,17] Our results showed that RV function as assessed by TDI derived MPI is significantly impaired in predialysis patients.

Reliable assessment of RV with conventional echocardiography is difficult because of the complex anatomy of RV. RV systolic function can be evaluated using several parameters: tricuspid annular plane systolic excursion (TAPSE); fractional area change; EF; the rate of pressure rise in the RV (dp/dt); MPI; systolic velocity of the tricuspid annulus; and longitudinal strain and strain rate.[18] Among these parameters, studies have demonstrated the clinical utility and value of MPI, TAPSE, fractional area change, and systolic velocity of the tricuspid annulus.[18] MPI is one of the accurate indices of ventricular performance since it is a combined index of systolic and diastolic functions independent of age, ventricular geometry, or heart rate.[19] This approach is reproducible and feasible in a large majority of subjects both with and without tricuspid regurgitation.[18] As myocardial function deteriorates, ejection time is shortened and the preejection and isovolumic relaxation intervals are lengthened. Obtaining MPI by tissue Doppler rather than the pulsed Doppler method allows measuring of all time intervals from a single cardiac cycle using one imaging view.

Prevalence of RV dysfunction among ESRD in our study is 56%. Noteworthy, 44% of patients exhibited MPI-RV $>$ 0.55; the upper reference limit of MPI as per ASE guidelines.[18] In a TDI study that assessed RV function in ESRD patients on long-term dialysis, RV dysfunction (defined as MPI $>$ 0.53) was identified in 65.8% of patients and its prevalence was higher in the hemodialysis group compared to the peritoneal dialysis group (71.3% vs. 34.6%, $P < 0.001$).[4] The high prevalence of RV dysfunction in our study may be attributed to the substantially high prevalence of systemic hypertension (83%; with uncontrolled pressure in many patients) and LV hypertrophy among our patients. Systemic hypertension and related LV hypertrophy were reported to be associated with RV dysfunction.[20,21] ESRD patients did not show significant change in s′-wave velocity which is a measure for RV systolic function. This does not contradict the usefulness of MPI which is an index for both systolic and diastolic functions (i.e., ventricular performance) while s′-wave velocity assesses systolic function at a single segment that may not truly represent the function of the entire RV. Moreover, the MPI integrates isovolumic and ejection phase indices and, therefore, may become abnormal before an ejection phase indices, such as s′-wave velocity, indicates an abnormality. These may explain the previously reported superior sensitivity of MPI (100%) compared to s′-wave velocity (59%) for detecting RV EF less than 50%.[22]

ESRD patients in this study showed significant diastolic dysfunction as evident by the lower e′-wave velocity and e′/a′ ratio. One of the potential mechanisms for impaired RV diastolic function is pulmonary hypertension. Chronic RV pressure overload often results in RV diastolic dysfunction with prolonged diastolic relaxation times and increased diastolic stiffness.[23,24] Furthermore, diastolic dysfunction is linked to myocardial fibrosis which is particularly high in patients with ESRD because of hypertension, increased volume and hyperparathyroidism.[25,26]

Several pathophysiologic mechanisms may adversely affect RV function and impair its adaptation mechanisms: activation of renin–angiotensin–aldosterone system; sympathetic activation; oxidative stress; inflammation with increased circulating cytokines; endothelial dysfunction; anemia and erythropoietin deficiency; and dysregulation of calcium–phosphorus balance.[27,28,29] All these mechanisms are further

accentuated through associated comorbidities (e.g., hypertension, diabetes).

Pulmonary hypertension was reported in 8–40% of predialysis patients.[16,30,31] In our study, pulmonary hypertension was detected in 36.5% of patients. There are several potential mechanisms that may contribute for the development of pulmonary hypertension in patients in ESRD: vasoconstriction of pulmonary vessels secondary to neurohormonal and metabolic derangement; LV diastolic dysfunction; increased stiffness of the pulmonary vasculature secondary to calcification; and high cardiac output induced by anemia.[32]

The lack of correlation between MPI-RV and calculated MPAP as well as the absence of significant difference in MPI-RV between patients with and without pulmonary hypertension argues against a major role for pulmonary hypertension in the development of RV dysfunction in ESRD patients. However in a study by Paneni et al., MPI-RV showed significant correlation with PASP ($r = 0.45$, $P < 0.01$) among ESRD undergoing long-term hemodialysis (mean duration of 43 months).[4] Nevertheless, the relation between RV dysfunction and pulmonary hypertension may be confounded by the presence of atriovenous fistula in their patients on long-term dialysis. Hemodynamic burden posed by the flow through atriovenous fistula can independently contribute to the development of both RV dysfunction and pulmonary hypertension.[4,16] Interestingly, in the same study by Paneni et al., when analysis was adjusted for pulmonary pressure, hemodialysis treatment was independently associated with MPI-RV.[4]

In accord with other studies, LV function as assessed with MPI was significantly impaired in patients with chronic kidney disease.[33,34] In our study, the high prevalence of systemic hypertensions and LV hypertrophy may contribute to subclinical LV dysfunction noticed in ESRD patients. Although LV hypertrophy may provide a compensatory mechanism for the increased afterload (caused by systemic hypertension), maladaptive structural changes may ultimately result in development of diastolic and systolic dysfunction. Although LV dysfunction may contribute to the development of RV dysfunction through multiple mechanisms,[3] the lack of significant correlation between MPI indices of LV and RV in our study argues against a major role of LV dysfunction in the development of RV dysfunction.

The study is predominantly limited by the small number of patients recruited. Small number is attributed to the many exclusion criteria used in the study protocol to rule out many confounding variables that may affect RV function. The MPI was recommended by ASE not to be used as the sole quantitative method for evaluation of RV function.[18] However, due to our small sample size, it would have been difficult to assess RV function using a strict dichotomous definition that utilizes two different cutoff points and this would be desirable to check in a larger cohort study. Given that MPI is load dependent,[35] volume overload in predialysis ESRD patients may skew the MPI. The same may apply for medications that affect preload and afterload (e.g., diuretics and ACE-I). Patients with clinical CAD were excluded from the study; however, this was not confirmed with coronary angiography in all patients. The effects of volume overload and other factors such as parathyroid hormone, phosphorus, neurohormonal profile, inflammation, and oxidative stress on RV function were not assessed in this study and more research is recommended in these regards. Pulsed TDI velocities were used in this study rather than the newer TDI derivatives of strain and strain rate. However, strain and strain rate indices may be less representative of global RV function. Diagnosis of pulmonary hypertension should be based upon right heart catheterization. However available literature on pulmonary hypertension in ESRD patients is based mainly on echocardiography.

In conclusion, subclinical RV dysfunction—as estimated by TDI derived MPI—is highly prevalent among ESRD patients even before starting dialysis therapy. Large prospective follow up study is needed to confirm whether predialysis ESRD patients with RV dysfunction are at a higher risk for developing congestive heart failure with long-term dialysis.

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