Study of Ventricular Interdependence in Hemodialysis Patients

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Abstract

Background and objectives

Study of respiratory variations in mitral valve (MV) Doppler flow in hemodialysis (HD) patients has not been investigated and normal adult referenced echocardiographic value is used as an echocardiographic reference to HD patients who have unique hemodynamic. This work aimed to study the respiratory variation in MV Doppler flow in HD patients to determine if it has a unique pattern in these patients, and to study any relation between this variation and volume-related parameters.

Methods

We conducted a prospective cohort study, carried out on 118 patients who underwent regular HD. A standard echocardiography was performed on the patients before and within 6 hs after dialysis. During quiet breathing, the transmitral spectral Doppler E wave was measured during inspiratory and expiratory phases using plethysmography breath-cycle chest-adhesive electrodes. The mathematic differences and the percent changes (ventricular interdependent; VI) in E wave were calculated pre-and post-dialysis. Post dialysis difference in the percent changes (Δ E wave % changes) was calculated as follows: pre-dialysis percent changes of E wave – post dialysis percent changes of E wave/pre dialysis percent changes E wave x 100.

Results

The means of the mathematic differences between the MV inspiratory and expiratory E pre-and post-dialysis were 0.07 ± 0.18 m/s and 0.08 ± 0.22 m/s respectively with an insignificant difference between both phases; p = 0.337. Meanwhile, the means of the percent variation in the MV inspiratory and expiratory E pre-and post-dialysis were 56 ± 7 % and 44 ± 1.1 % respectively, with a significant reduction after dialysis; P = 0.000. Spearman correlation showed a significant positive correlation between post-dialysis Δ E wave % change and post-dialysis % change of weight (r = 0.318; P = 0.000). Moreover, post-dialysis % change of weight and post- dialysis % changes of most other volume-related variable were independent predictors of post- dialysis Δ E wave % in HD patients.

Conclusion

The pre- and post- dialysis respiratory changes in the MV E wave in HD patients were higher than the normal adult referenced values. This marked variation could be explained by the unique overloading condition and could explain the LV diastolic dysfunction and the unexplained pulmonary hypertension in HD patients.

1 Introduction

HD patients have high cardiovascular morbidity and mortality, and their adjusted risk of death is about 10 to 20 times higher than the general population [1]. Echocardiography is a noninvasive imaging technique

that has been extensively used to study the morphological and the functional cardiac changes in HD patients [2]. The echocardiographic parameters that commonly measured are left ventricular (LV) systolic, LV diastolic function, RV function, and pulmonary hypertension. The changes in these parameters have been linked to both traditional CV risk factors, which are more prevalent in HD patients, and uremic milieu related factors [3].

Respiration induces cyclic physiological modification of intracardiac hemodynamics. Moreover, as the pericardium has a constraining effect on the combined volume of the four cardiac chambers, respiratory variation in intrapericardial pressure results in reciprocal variation in the filling of both ventricles [5]. With inspiration, intrathoracic and intrapericardial pressures decrease. This augments right ventricular filling and stroke volume and, as the total pericardial space is limited, a compensatory decrease in left ventricular stroke volume occurs in inspiration [4]. With expiration, the opposite occurs. Under normal circumstances, the Doppler peak velocity of mitral valve (MV) inflow varies by 15% or less with respiration and tricuspid inflow by 25% or less [5]. The study of respiratory variation in MV Doppler flow in patients who undergo HD has not been investigated and the normal adult referenced echocardiographic value of respiratory variation in MV Doppler flow is used as an echocardiographic reference to HD patients, who have unique hemodynamics related to the pre-dialysis overloading condition and the cyclic changes in their volume status induced by ultrafiltration. The current study aimed to study the respiratory variation in MV Doppler flow in HD patients, to determine if it has a unique pattern in these patients, and to study any relation between these variations and volume-related parameters.

2 Patients And Methods

2.1 Study design

This was a prospective cohort study, carried out on HD patients who underwent regular HD in the Nephrology Unit of Assiut University Hospital.

2.2 Ethical considerations

The study was approved by the Ethical Committee of the College of Medicine of Assiut University. Written informed consent was obtained from the patients themselves before their inclusion; illiterate participants gave their consent by fingerprints.

2.3 Patients

This study was carried out on 118 regular HD patients from January 2018 to September 2018. Eligible patients were adults aged 18 years or older.

Exclusion criteria were patients with poor echo window, non-sinus rhythm, congenital heart disease, rheumatic heart disease, left ventricular systolic dysfunction (EF < 40 %), impaired RV systolic function (TAPSE < 1.5 cm), pericardial effusion, obviously thickened and/or echogenic pericardium, calcific pericardium with lateral chest x-ray, patients with chronic lung disease (either by history, abnormal

imaging, abnormal arterial blood gases or pulmonary function test), mediastinal syndrome, and patients with pneumonia or respiratory distress.

2.4 Methods

All patients underwent echocardiography with an HDI 5000 instrument (Philips Medical Systems, Bothell, Washington, USA) equipped with a broadband harmonic transducer. All echocardiographic examinations were carried to the patients before the hemodialysis sessions and within 6 hours after the sessions. Standard echocardiography was done based on apical four and two-chamber views. All echocardiograms were carried out at the Internal Medicine Department of Assiut University Hospital. LV dimensions were calculated using 2D guided M- mode calculations. The mean value of three measurements of the technically best cardiac cycles was taken from each examination. LV EF was measured by 2D guided M-mode calculations. The LV diastolic function was calculated using transmitral E wave velocity using 2D guided spectral pulsed Doppler with a sample size of 0.7 mm just above MV leaflets tips. RV systolic function was measured using tricuspid annular plane systolic excursion (TAPSE) using M-mode.

During quiet breathing, the transmitral spectral Doppler E wave was measured during inspiratory and expiratory phases. After at least 3 respiratory cycles with the aid of Plethysmographic breath cycle chest adhesive electrodes of a separate monitor (GE Medical Systems, Milwaukee, Wisconsin, USA), the best and complete E wave velocity envelope in each respiratory phase was measured (Figure: 1).

The pre-and post-dialysis mathematic difference in E wave were calculated as follows: expiratory E wave - inspiratory E wave in each phase. The pre- and post-dialysis respiratory percent changes of MV E wave which represents the degree of ventricular interdependence was calculated as follows: expiratory E wave - inspiratory E wave / expiratory E wave x 100. Post dialysis difference in the percent changes (Δ E wave % changes) was calculated as follows: pre-dialysis percent changes of E wave – post dialysis percent changes of E wave/pre dialysis percent changes E wave x 100.

2.5 Hemodialysis/Ultrafiltration volume data

Haemodialysis was performed using Fresenius 5008 therapy system (Fresenius Medical Care). The average duration of dialysis was about 4 hours. Dialysate temperature was kept constant at 37°C with dialysate ion-concentrations consisting of Na^+ 140 mmol/L, HCO^{3-} 38 mmol/L, K^+ 2.0 mmol/L, and Ca^{2+} 1.25 mmol/L. Filters used were PF 170 or PF 210 from Gambro. The average blood flow was 300 mL/m. Dialysate flow was set at 500 mL/m. Blinded resident nephrologists, guided by the standard HD unite protocols, estimated the ultrafiltration volumes of the included patients.

2.6 Data collection

Patients' demographic data and medical history including age, sex, and comorbid diseases were recorded. Body mass index (BMI) was calculated as (weight (kg)/ height^2 (m)). The following clinical variables were measured before and within 6 hours after dialysis: systolic and diastolic blood pressure by mercurial sphygmomanometer in a head and arm supported supine position after 10 minutes of rest; heart rate; the presence of lower limb edema; the presence of congested neck veins; and the presence of

basal lung rales. Venous blood samples were collected from the studied patients before and after the end of dialysis sessions to measure the followings: serum levels of creatinine (mg/dl), urea (mg/dl), Hb (g/dl), Na (mmol/l), and K (mmol/l) levels. A Sonosite M-TURBO ultrasound machine with a 3.5 MHz frequency probe was used to detect IVC diameter. The probe was placed in the subxiphoid location when the patients were supine. The IVC was measured 2 cm caudal to the junction point of the hepatic vein and IVC. Both the inspiratory and respiratory diameters were detected by measuring the vein lumen at 1 respiratory cycle, from 1 interior wall to the opposite interior wall. Percent changes of these variable were calculated as follow: pre-dialysis value – post-dialysis value / post-dialysis value %.

2.7 Statistical analysis

The statistical analysis was performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to test normality. The continuous variables were presented as the means ± SD or median and range, and categorical variables were presented as frequency and percentage. Chi-square test and Fisher Exact test were used to compare qualitative parameters. The paired t-test was used to determine changes between quantitative parameters before and after dialysis in case of parametric variables and Wilcoxon Signed Rank test in case of non-parametric variables. Spearman correlation was used to test the presence of correlation between Δ E wave % change and % change of weight. Univariate regression analysis was used to detect the relations between Δ E wave % changes and other variables while multivariate regression analysis was used to detect the independent predictors of Δ E wave % changes. A p-value < 0.05 was considered statistically significant.

3 Results

3.1 Demographic data

The mean age of the study population was 53.46 ± 9.55 (years). Other demographic data were shown in table 1.

3.2 Clinical and laboratory data

The mean ultrafiltration dose was 3.27 ± 1.53 Liter/session. There were statistically significant reductions of post-dialysis systolic BP, diastolic BP, RR, weight, urea, creatinine, and serum K+. While there was no case with pulmonary congestion after dialysis and no significant reduction in the presence of lower limb edema, the presence of pleural effusion, serum Na + and HB (Table:2).

3.3 Pre and post dialysis echocardiographic and IVC data

There were significant reductions in all cardiac chambers' dimensions, inspiratory and expiratory trans-mitral and trans-tricuspid Doppler flow waves, PASP, and both inspiratory and expiratory IVC diameters. While there were significant increases in LV EF and TASPE after dialysis (Table: 3).

3.4 Respiratory changes

The means of the mathematic differences in the MV inspiratory and expiratory E pre-and post-dialysis were 0.07 ± 0.18 m/s and 0.08 ± 0.22 m/s respectively with an insignificant difference between both phases; p = 0.337. Meanwhile, the means of the percent variation in the MV inspiratory and expiratory E pre-and post-dialysis were 56 ± 7 % and 44 ± 1.1 % respectively, with a significant reduction after dialysis; P = 0.000 (Figure:2). The post-dialysis Δ MV E wave % change after dialysis was 22.74 ± 14.98 (-15.25-70.21). Moreover, the means of the mathematic differences in the TV inspiratory and expiratory E pre-and post-dialysis were 1.09 ± 0.34 m/s and 1.19 ± 0.48 m/s respectively with an insignificant difference between both phases; p = 0.427. Meanwhile, the means of percent variation in the TV inspiratory and expiratory E pre-and post-dialysis were 67 ± 18 % and 54 ± 17 % respectively, with a significant reduction after dialysis; P = 0.000. The post-dialysis Δ TV E wave % change after dialysis was 31.21 ± 17.38 (-13.62-82.31) (Table: 3).

Correlation and Regression analysis

Spearman correlation showed a significant positive correlation between post-dialysis Δ E wave % change and % change of weight (r = 0.318; P = 0.000) (Figure:3). Moreover, univariate analysis showed a significant relation between post-dialysis Δ E wave % change and percent change of weight, systolic BP, diastolic BP, plasma urea, HB, serum Na +, and both inspiratory and expiratory IVC diameters (Table:4). While multivariate analysis showed that the independent predictors of post-dialysis Δ E wave % change were the change of weight, systolic BP, diastolic BP, plasma urea, creatinine, HB, serum Na +, serum K+, LV EDD, PASP, and both inspiratory and expiratory IVC diameters (Table:5).

4 Discussion

The main findings in this study are (1) the means of the percent respiratory variation in MV E wave were 56 ± 7 % pre-dialysis, and 44 ± 1.1 % post-dialysis, (2) there was a significant reduction in Δ E wave % change after dialysis, (3) the post-dialysis Δ E wave % change was significantly related to volume-load reduction parameters after dialysis.

Both left and right ventricles are interdependent because they are enclosed within the pericardium and have the septum in common [6,7]. During spontaneous inspiration, increased venous return to the right heart increases the right ventricular end-diastolic volume (RVEDV) which shifts the septum to the left and reduces left ventricular end-diastolic volume (LVEDV) [8]. It is well known that with spontaneous respiration small changes (< 15%) in trans-mitral peak flow velocities occur in healthy subjects [5].

The current study detects higher percent variations in MV E wave than that has been referenced for normal adults. The exaggerated ventricular interdependence in HD patients could be explained by the increase in the degree of pericardium constrain in HD patients. This could be produced by uremia and other subtle changes in the pericardial tissue that could not be detected by conventional methods. In a constricting pericardium, the interventricular interaction increases, so that with RV volume increase, there

is a corresponding decrease in LV volume [9]. Hypervolemia in patients with constrictive pericarditis reduces the respiratory variation of the Doppler inflows and exaggerated ventricular interdependence may not be detected unless preload is reduced by head-up tilt or diuretics [10]. However, the current study showed that respiratory variation in MV E wave was reduced after ultrafiltration which makes the explanation by pericardial constriction unacceptable.

Another explanation of the exaggerated ventricular interdependence in HD patients could be that: the interdialytic weight gain could mainly have a predominant effect on the RV which causes its significant inspiratory expansion that in turn makes marked inspiratory shift in the IVS shifts to the LV. This explanation is supported by the significant reduction in the percent variation after dialysis.

It is well known that echocardiographic measurements are affected by the changing LV loading conditions during hemodialysis [11,12,13,14]. The current study could point to another cardiac overloading consequence of interdialytic weight gain which is the exaggerated ventricular interdependence. The hemodynamic effect of this exaggerated respiratory variation and marked IVS shift, especially before dialysis, may add another cause for the impairs the LV diastolic function in HD [11,12,13,14,15,16]. Impaired LV filling leads to chronic pulmonary congestion and hence pulmonary hypertension would develop. It may unveil one of the hidden mechanisms of idiopathic pulmonary hypertension in HD patients named as group 5 ‘unexplained PHT’ by WHO [17,18].

In the current study, there was a significant improvement in lung rales post-dialysis. This reflects the effective value of ultrafiltration as a LV unloading therapy and it is in concordance with the AHA/ACC and ESC guidelines that consider ultrafiltration as a reasonable therapy in decompensated heart failure patients with unresolved congestion who cannot withstanding optimal medical therapy and/or hyponatremia [19,20].

Ultrafiltration during HD comprises intravascular volume mobilization using osmotic or hydrostatic pressure. It has been reported that cardiac chambers dimensions decrease in response to volume loss [21,22] and also in response to ultrafiltration [11,12,13,14] in agreement with the findings of the current study.

In the current work, there were a significant reduction in both IVC inspiratory and expiratory diameters after dialysis. A meta-analysis done by Dipti et al [23] reported that IVC diameter is consistently low in hypovolemic status when compared with euvolemic. Moreover, IVC diameter was significantly decreased after blood donation [24]. However, during the management of heart failure, there were no significant changes in the IVC size with time [25]. This could be explained by the phenomenon of vascular refilling which means that rapid vascular refill could mask the IVC diameter changes related to volume loss. In the current work, measurement of IVC diameter was done within 6 hours, which could be fast enough to detect the rapid volume changes before the refill phenomenon could mask it.

5 Conclusion

The percent respiratory variation in the MV E wave was higher than the normal adult referenced percentage both pre- and post- dialysis in HD patients. This marked variation could be explained by the unique overloading condition and could explain the LV diastolic dysfunction and the unexplained pulmonary hypertension in HD patients.

6 Study Limitations And Recommendations:

The current work was not without obvious remarks. Firstly, the work was conducted on HD patients without control group and compare the respiratory variation between the included patients and the used reference value. However, to exclude confounders in the study we should have include a control group. Secondly, the work was conducted on a mono-ethnic patient and its results cannot be used as a generalized reference, so, we recommend studying this phenomenon in multi-ethnic scale. Thirdly, subclinical pericardial constrain is still a remarkable confounder, so, we recommend using multidetector CT or cardiac MRI to detect any pericardial abnormalities in HD patients to be sure they do not have any subtle pericardial contain before inclusion. Lastly, the current work was single-center non-outcome-based studies, and we suggest conducting a multi-center prognosis-based study to detect the prognostic value of this phenomenon in HD patients.

Declarations

Not applicable

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Conflict of interests:

The authors declare that there was no conflict of interest as regards the publication of this paper.

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Tables

Table (1): Demographic data and risk factors of the study population

	No. (118)	%
Age		
< 50	47	39.8
50 – 60	39	33.1
> 60	32	27.1
Female	50	42.4
BMI:		
Normal (< 25 kg/m^2)	74	62.7
Overweight (> 25 kg/m^2)	44	37.3
Risk factors:		
HTN	84	71.2
D.M	48	40.7
Smoking	44	37.3

BMI: Body mass index (kg/m^2), HTN: systemic hypertension, DM: diabetes mellites

Table (2): Clinical and laboratory data pre-and post-dialysis

	Pre-dialysis	Post-dialysis	P-value
Systolic BP (mmhg)	137.37 ± 14.76	120.08 ± 8.82	*0.000*
Diastolic BP (mmhg)	89.07 ± 9.56	78.56 ± 5.67	*0.000*
Heart rate (b/min)	80.47 ± 5.88	73.39 ± 4.71	*0.000*
Lower limb edema no (%)	11 (9.3%)	11 (9.3%)	*1.000*
Pleural effusion no (%)	6 (5.1%)	6 (5.1%)	*1.000*
Pulmonary congestion no (%)	30 (25.4%)	0 (0.0%)	*0.000*
Weight (kg)	71.44 ± 6.94	68.63 ± 6.81	*0.000*
Creatinine (mg/dl)	10.41 ± 2.19	4.76 ± 1.02	*0.000*
Urea (mg/dl)	138.44 ± 24.99	59.64 ± 13.49	*0.000*
H.B (g/dl)	8.88 ± 0.90	8.75 ± 0.85	*0.203*
Na (mEq/dl)	137.38 ± 3.91	136.91 ± 1.73	*0.180*
K (mEq/l)	4.56 ± 0.52	3.31 ± 0.16	*0.000*

BP: blood pressure, HB: hemoglobin, Na: serum sodium, K: serum potassium,

Table (3): Echocardiographic data pre-and post-dialysis

	Pre-dialysis	Post-dialysis	P-value
MV Inspiratory E wave (m/s)	1.19 ± 0.16	0.93 ± 0.28	0.000
MV Expiratory E wave (m/s)	1.25 ± 0.20	1.00 ± 0.44	0.000
MV E wave respiratory difference (m/s) *	0.07 ± 0.18	0.08 ± 0.22	0.337
	(-0.31 - 0.29)	(-0.19 - 0.50)	
MV E wave respiratory variations (%) **	56 ± 7	44 ± 1.1	0.000
	(36 - 74)	(14 - 68)	
TV Inspiratory E wave (m/s)	2.34 ± 0.21	1.43 ± 0.21	0.000
TV Expiratory E wave (m/s)	1.64 ± 0.27	1.01 ± 0.24	0.000
TV E wave respiratory difference (m/s) ^	1.09 ± 0.34	1.19 ± 0.48	0.427
	(-0.02 - 1.48)	(-0.03 - 1.71)	
TV E wave respiratory variations (%) ^^	67 ± 18	54 ± 17	0.000
	(41-81)	(21-71)	
LAD (cm)	3.69 ± 0.67	3.00 ± 0.62	0.000
RVEDD (cm)	1.97 ± 0.17	1.77 ± 0.18	0.000
LVEDD (cm)	49.40 ± 6.15	56.75 ± 7.86	0.000
LVESD (cm)	32.67 ± 5.04	36.36 ± 5.11	0.000
LVEF (%)	55.96 ± 5.60	67.70 ± 4.83	0.000
TAPSE (cm)	2.50 ± 0.44	2.77 ± 0.56	0.001
End inspiratory IVCD (cm)	1.21 ± 0.32	1.01 ± 0.33	0.000
End expiratory IVCD (cm)	1.77 ± 0.30	1.44 ± 0.30	0.000
PASP (mmhg)	20.25 ± 2.66	15.30 ± 2.49	0.000

LAD: left atrium diameter, RVEDD: right ventricle end-diastolic diameter, LVEDD: left ventricle end-diastolic diameter, LVESD: left ventricle end-systolic diameter, IVCD: inferior vena cava diameter, PASP: pulmonary artery systolic pressure.

* MV expiratory E wave minus inspiratory E wave (m/s), mean, standard deviations and range.

** MV respiratory percent changes, mean, standard deviations and range.

^ TV inspiratory E wave minus expiratory E wave (m/s), mean, standard deviations and range.

^^ TV respiratory percent changes, mean, standard deviations and range.

Table (4): Univariate linear regression analysis

	t	P-value	95.0% CI for B	
			Lower	Upper
Weight % change (kg)	3.613	0.000	1.027	3.520
Systolic B.P. % change (mmhg)	2.731	0.007	0.126	0.794
Diastolic B.P. % change (mmhg)	3.154	0.002	0.176	0.771
Creatinine % change (mg/dl)	-0.724	0.471	-0.550	0.255
Urea % change (mg/dl)	-2.646	0.009	-1.118	-0.161
H.B % change (g/dl)	4.627	0.000	4.147	10.355
Na. % change (mEq/dl)	-2.667	0.009	-3.199	-0.473
K % change (mEq/dl)	1.575	0.118	-0.084	0.738
LAD % change (cm)	1.654	0.101	-0.070	0.783
RVEDD % change (cm)	0.906	0.367	-0.219	0.588
LVEDD % change (cm)	1.250	0.214	-0.188	0.833
LVESD % change (cm)	-1.916	0.058	-1.051	0.018
LVEF % change (cm)	-1.899	0.060	-0.748	0.016
End inspiratory IVCD % change (cm)	-6.361	0.000	-1.316	-0.691
End expiratory IVCD % change (cm)	5.507	0.000	0.933	1.982
PASP % change (mmhg)	-1.374	0.172	-1.215	0.220

Dependent variable: ΔE wave % changes

B.P: blood pressure, HB, hemoglobin, Na: serum sodium, K: serum potassium, LAD: left atrium diameter, RVEDD: right ventricle end-diastolic diameter, LVEDD: left ventricle end-diastolic diameter, LVESD: left ventricle end-systolic diameter, IVCD: inferior vena cava diameter, PASP: pulmonary artery systolic pressure.

Table (5): Multiple linear regression analysis

	t	P-value	95.0% CI for B	
			Lower	Upper
Weight % change (Kg)	4.595	0.000	0.421	1.061
Systolic B.P. % change (mmhg)	-2.936	0.004	-0.308	-0.060
Diastolic B.P % change (mmhg)	4.126	0.000	0.117	0.333
Creatinine % change (mg/dl)	4.498	0.000	0.149	0.384
Urea % change (mg/dl)	-6.342	0.000	-0.533	-0.279
H.B % change (g/dl)	1.010	0.315	-0.706	2.171
Na % change (mEq/dl)	-1.740	0.085	-0.652	0.043
K % change(mEq/dl)	-3.121	0.002	-0.246	-0.055
LAD % change (cm)	-3.373	0.001	-0.247	-0.064
RVEDD % change (cm)	-1.297	0.198	-0.209	0.044
LVEDD % change (cm)	-5.560	0.000	-0.454	-0.215
LVESD % change (cm)	-2.047	0.043	-0.287	-0.005
LVEF % change (%)	3.348	0.001	0.095	0.372
End inspiratory IVCD % change (cm)	-44.352	0.000	-2.027	-1.853
End expiratory IVCD % change (cm)	28.804	0.000	2.752	3.159
PASP % change (mmhg)	-2.440	0.016	-0.430	-0.044

Dependent variable: ΔE wave % changes

B.P: blood pressure, HB, hemoglobin, Na: serum sodium, K: serum potassium, LAD: left atrium diameter, RVEDD: right ventricle end-diastolic diameter, LVEDD: left ventricle end-diastolic diameter, LVESD: left ventricle end-systolic diameter, IVCD: inferior vena cava diameter, PASP: pulmonary artery systolic pressure.