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Comparison of lung ultrasound and other volumetric methods in peritoneal dialysis patients

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Abstract

Although many alternative methods are present, maintaining ideal volume status in peritoneal dialysis (PD) patients still rely on clinical evaluation due to lack of an evidence-based method. Lung ultrasound (LUS) is a new method for evaluation of hidden congestion in this group.

LUS findings and its relationship with other volumetric methods are investigated in this observational cross-sectional study.

In this observational cross sectional study, LUS was performed to all PD patients and compared with symptoms of hypervolemia, physical examination, vascular endothelial growth factor-C (VEGF-C), and N-terminal pro-brain natriuretic peptide levels, chest radiography, echocardiography, bioelectrical impedance analysis.

Data of 21 PD patients were evaluated. There was correlation between number of B lines and VEGF-C levels ($r = 0.447$, $P = .042$), daily urine output ($r = 0.582$, $P = .007$) and left ventricle mass index ($r = -0.456$, $P = .038$). Correlations with all other parameters were not significant. Daily urine output and VEGF-C levels were significantly different when B lines were grouped into 2 according to the median level ($P < .05$ for all).

This is the widest spectrum study looking for LUS findings and other volumetric parameters in a small PD cohort. LUS might be useful to evaluate hidden hypervolemia. Its correlation with VEGF-C level is a novel finding.

Abbreviations: BIA = bioelectrical impedance analysis, LUS = lung ultrasound, LVMI = left ventricle mass index, NT-proBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Association, PD = peritoneal dialysis, VEGF-C = vascular endothelial growth factor-C.

Keywords: hypervolemia, lung ultrasound, peritoneal dialysis, vascular endothelial growth factor-C, volume control

1. Introduction

Maintaining volume control is crucial in all renal replacement therapy modalities. Fluid overload is associated with increased mortality both in hemodialysis patients[1] and peritoneal dialysis (PD) patients[2] although PD has the advantage of better preservation of residual renal function compared to hemodialysis.[3] Many methods have been used to fine tune the volume status of patients including physical examination, chest radiography, blood pressure, laboratory parameters, echocardiography, bioelectrical impedance analysis (BIA), ultrasound for lung.[4]

Symptoms of hypervolemia are mainly paroxysmal nocturnal dyspnea, orthopnea, edema, dyspnea on exertion. On physical examination, hypertension or hypotension, third heart sound, jugular venous distension, rales, edema can be seen.[5] Pulmonary venous congestion, cardiomegaly, interstitial edema, alveolar edema, pleural effusion can be seen on chest radiographs.[5]

Level of N-terminal pro-brain natriuretic peptide (NT-proBNP) increases upon stretching of cardiac myocytes. This is accepted as a reflection of volume status. There are a few studies in which NT-proBNP was found as a useful marker for hypervolemia both in hemodialysis[6] and PD population.[7]

Vascular endothelial growth factor-C (VEGF-C) is an osmosensitive gene product secreted by macrophages through activation of tonicity-responsive enhancer binding protein found in mononuclear phagocyte system cells infiltrating the intersti-

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Subjects (or their parents or guardians) have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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tium. The result is hypertonic sodium accumulation in the skin which is accepted as a buffer mechanism maintaining blood pressure homeostasis.[8] Serum VEGF-C levels had been found as a promising marker of hypervolemia in a hemodialysis patient cohort by Sahutoglu et al.[9]

Echocardiography has been used extensively in dialysis patients in which a number of parameters have been measured.[10] BIA is another non-invasive bedside method for the evaluation of volume status.[11]

Lung ultrasound (LUS) is a technique that has become popular in nephrology recently. "B lines" or "lung comets" are the reverberation artifacts arising from the pleural line. They are produced due to thickened subpleural interlobular septa by edema.[4]

The gold standard for volume assessment is isotope dilution and neutron activation analysis methods which are only limited to research activities. The best widely accepted, non-invasive, practical, easy to access method has not been decided yet. Moreover, the evidence is quite scarce for the PD than hemodialysis or normal renal functioning group. LUS is the most recent promising method for volume control.

We aimed to define LUS findings in our PD cohort and its relation with other volumetric parameters.

2. Materials and methods

This study was approved by local ethics committee and registered to Clinical Trials. Ethical approval number is 957. Clinical Trials number is NCT03801044. All participants provided informed consent form.

All PD patients in our clinic have been invited to the study. Exclusion criteria were patients younger than 18 years old, unwilling to participate to the study, immobile patients unable to perform tests in the same day, history of PD less than 3 months, the presence of active infection, history of lung cancer and/or lung operations.

All enrolled patients answered the questions about hypervolemia symptoms, had physical and laboratory examination, chest radiography, echocardiography, BIA and LUS on the same day.

2.1. Demographic characteristics

Data regarding demographic characteristics, ESRD etiology, past and present medical history was taken from patients' medical files.

2.2. Hypervolemia symptoms and physical examination

Patients were asked for orthopnea, dyspnea at rest, effort dyspnea, paroxysmal nocturnal dyspnea. They had a physical examination including height, weight, blood pressure measurement, the definition of New York Heart Association (NYHA) class, the presence of third heart sound (S3), crackles, pretibial edema. Edema was classified as present or absent.

2.3. Laboratory

VEGF-C levels were measured in the serum samples. R&D Systems kit (Minneapolis, MN) (Catalog Number DVEC00) was used for the assays according to the user instructions. NT-proBNP was measured on the Elecsys 2010 analyzer (Elecsys proBNP Immunoassay; Roche Diagnostics).

2.4. Chest radiography

All radiographs were taken when the patient was standing erect position during deep inhalation. They were reported by an expert radiologist blinded to clinical data. Films taken at a supine position or during expirium were excluded. Chest radiographs were classified into 3 stages to reflect a degree of hypervolemia.[12] Stage 1 was redistribution defined as an increased artery-to-bronchus ratio in the upper and middle lobes. Stage 2 was interstitial edema evident by Kerley B lines and peribronchial cuffing. Stage 3 was alveolar edema phase perihilar consolidation and air bronchograms, pleural fluid, the increased width of the vascular pedicle, enlarged cardiac silhouette.

2.5. Echocardiography

Transthoracic echocardiography was performed by the same cardiologist blinded to all other parameters. It was done while the abdomen was empty. LV end diastolic diameter (mm), interventricular septum thickness (mm), posterior wall thickness (mm), ejection fraction (%), left ventricle end diastolic volume (mL), left atrial volume (mL), left ventricle mass index (LVMI) (g/m^2), left ventricle filling velocity (cm/sec), E/E' ratio, pulmonary artery systolic pressure (mm Hg) were the parameters taken by echocardiography.[13]

2.6. BIA

The Body Composition Monitor (type 0BJA1394, Fresenius Medical Care AG & Co. KGaA, D-61343 Bad Homburg) was used for assessment of hydration status in patients. Peritoneal cavities were free of intraperitoneal fluid during measurement.[14] Patients were accepted as normovolemic if their result were between –1.1lt and 1.1 lt.[15]

2.7. LUS

It was performed by 28 area method which contains ultrasound examination from second to fifth intercostals spaces at the parasternal region, midclavicular line, anterior, and midaxillary lines.[16] LUS had been done by the same radiologist who was an expertise in ultrasonography blinded to all other parameters. It was performed by 1,6 MHz convex probe when a patient lying at the supine position.

2.8. Statistical analysis

All values were given as a median and interquartile range. Due to the limited number of patients, all data were accepted as abnormally distributed. Comparison of continuous variables was performed by the Mann–Whitney *U* test and comparison of categorical variables was done by Chi-Squared test. Correlation analysis was done by Pearson correlation test. *P* value was accepted as significant if less than .05. SPSS 21 (SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for statistical analysis.

3. Results

Twenty-three patients were enrolled in the study. Two patients were excluded from the study because of immobility.

3.1. Demographic characteristics

Twenty-one patients' data were examined. The median age for patients was 48 (38.5–66) years of which 81% was female. The

Table 1

Details of demographic characteristics, symptoms and signs of hypervolemia, bioelectrical impedance analysis, laboratory values and comparison of data according to B line groups.

	All patients	B line ≤1	B line>1	P
Age (yr), median (IQR)	48 (38.5-66)	57 (35.75–66.75)	47 (38.5–50.5)	.545
Female (%)	81	83.3	77.8	.748
ESRD etiology (%)				.316
Unknown	57.1	58.3	55.6	
Hypertension	9.5	8.3	11.1	
Diabetes mellitus	9.5	16.7		
FMF	4.8	8.3		
FSGS	9.5		22.2	
IgA nephropathy	4.8	8.3		
Tuberous sclerosis	4.8		11.1	
Duration of PD (mo), median (IQR)	22 (13–49.5)	21.5 (11.75–52.25)	27 (10–47.5)	.859
Coronary artery disease (%)	19	25	11.1	.422
Congestive heart failure (%)				NA
Daily urine volume (mL)	375 (125–1075)	225 (62.5–487.5)	875 (350–1775)	.025
Crackles (%)				NA
Edema				.422
Negative (%)	81	75	88.9	
S3, positive				NA
Systolic blood pressure (mm Hg), median (IQR)	140 (115–145)	140 (115–140)	140 (110–150)	.687
Diastolic blood pressure (mm Hg), median (IQR)	80 (80–90)	80 (80–80)	80 (75–90)	.353
Body mass index (kg/m^2), median (IQR)	26.7 (24.4–29)	28.31 (23.6–29.7)	26.37 (24.71–27.46)	.477
NYHA Class (%)				.375
Class I	95.2	91.7	100	
Class I	4.8	8.3		
PND (%)				NA
Ortopnea (%)	–	–	–	NA
Dyspnea (%)	–	–	–	NA
Effort dyspnea (%)				
Positive	19	25	11.1	.422
BIA (liter), median (IQR)	0.9 (0.1–2)	0.8 (0.075–2.05)	1.3 (0.1–2.1)	.522
NT-pro BNP (pg/mL), median (IQR)	2217 (624–5016)	3024 (568–9397)	2217 (885–3959)	.619
VEGF-C (pg/mL), median (IQR)	0.29 (0.23–0.34)	0.25 (0.21–0.32)	0.33 (0.27–0.35)	.039

BIA = body impedance analysis, ESRD = end stage renal disease, FMF = familial mediterranean fever, FSGS = focal segmental glomerulosclerosis, NT-proBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Association, PD = peritoneal dialysis, PND = paroxysmal nocturnal dyspnea, S3 = third heart sound, VEGF-C = vascular endothelial growth factor-C.

cause of the end-stage renal disease was hypertension in 9.5%, diabetes mellitus in 9.5%, Familial Mediterranean Fever in 4.8%, IgA nephropathy in 4.8%, tuberous sclerosis in 4.8%, and unknown in 57.1%. None of them had known congestive heart failure or coronary artery disease. The median duration of PD was 22 (13–49.5) months. Median daily urine volume was 375 (125–1075) mL. Patients with daily urine volume ≤100 mL were 25% of the total cohort. Details are given in Table 1.

3.2. Hypervolemia symptoms and physical examination

Patients did not report paroxysmal nocturnal dyspnea, orthopnea, resting dyspnea (Table 1). Majority of them (95.2%) were NYHA class I. Effort dyspnea was present in 19% of the cohort. On physical examination, median body mass index was 26.7 (24.4–29) kg/m^2. Median systolic and diastolic blood pressure was 140 (115–145), 80 (80–90) mm Hg, respectively. None of the patients had crackles or S3 heart sound. Pretibial edema was negative in 81% of patients.

3.3. Laboratory

Median VEGF-C level was 0.29 ng/mL (0.23–0.34 ng/mL). Median NT-proBNP level was 2217 pg/mL (624–5016 pg/mL) (Table 1).

3.4. Chest radiography

Two films were not classified due to incorrect position and exhalation, respectively. Most of the radiographies (78.9%) were classified as normal. On chest radiography examination, median cardiothoracic index was 0.46 (0.43–0.50) (Table 2).

3.5. BIA

Median BIA was 0.9 lt (0.1–2 lt) (Table 1). According to the BIA, 42.9% of the cohort was hypervolemic.

3.6. Echocardiography

Ejection fraction was 60% (57.5–65%). Median values for other echocardiographic parameters were given in Table 2.

3.7. LUS

The median number of B lines was 1 (0–5). B line was not present in 47.6% of patients. The number of B lines was similar according to the present co-morbidities (diabetes, hypertension, coronary artery disease), NYHA class, the presence of edema and effort dyspnea ($P > .05$ for all).

Table 2

Chest radiography and echocardiography findings of all patients and comparison of them with B line groups.

	All patients	B line ≤1	B line>1	P
Chest radiography (%)				
Normal	78.9	70	88.9	.294
Stage 1	10.5	10	11.1	
Stage 2	10.5	20	–	
Cardiothoracic index, median (IQR)	0.46 (0.43–0.50)	0.50 (0.44–0.54)	0.45 (0.43–0.47)	.06
Left ventricular end systolic diameter (cm), median (IQR)	4.7 (4.15–4.95)	4.75 (4.12–5.25)	4.3 (4.1–4.75)	.284
Interventricular septum thickness (cm), median (IQR)	1 (0.9–1.15)	1 (0.9–1.2)	1 (0.85–1.1)	.562
Posterior wall thickness (cm), median (IQR)	1 (0.9–1.1)	1 (0.9–1.1)	0.9 (0.85–1.05)	.536
Ejection fraction (%), median (IQR)	60 (57.5–65)	61 (49.75–65)	60 (60–62.5)	.941
Left ventricle end systolic volume (mL), median (IQR)	95 (83.5–132.5)	100 (76.75–128.75)	94 (87.5–135)	.887
Left atrial volume (mL), median (IQR)	37 (29–43)	36 (31–44.75)	37 (26–41)	.643
Left ventricle mass index (g/m^2), median (IQR)	95 (69.5–114.5)	100.5 (70.25–129.5)	75 (69.5–92)	.176
Left ventricle filling velocity (cm/sec), median (IQR)	78 (61.5–85.5)	78.5 (56.75–86.25)	74 (65–87)	.859
E/E', median (IQR)	11 (9.9–12.5)	11.6 (9.85–12.67)	10.7 (9.9–11.55)	.393
Pulmonary artery pressure (mm Hg), median (IQR)	25 (20–29)	24 (20–33.25)	24.33 (19–29)	.693
Left ventricle mass (gr), median (IQR)	153 (116.5–213)	172 (114–225)	136 (116.5–180)	.155

3.8. Grouping according to LUS

Patients are grouped into 2 according to the median B line as the number of B line is ≤1 and above 1. Details of the comparisons are given at Tables 1 and 2. Demographic characteristics, physical examination, echocardiography findings were similar between groups. VEGF-C level was 0.25 ng/mL (0.21–0.32 ng/mL) in patients with B line ≤1 whereas it was 0.33 ng/mL (0.27–0.35 ng/mL) in the other group ($P=.039$). Moreover, daily urine volumes were 225 mL (62.5–487.5 mL), 875 mL (350–1775 mL) in patients with B line ≤1 group and the other group, respectively ($P=.025$).

3.9. Correlation analysis between LUS and other parameters

There was statistically significant correlation between B lines and residual urine volume ($r=0.582$, $P=.007$), VEGF-C level ($r=0.447$, $P=.047$) and left ventricular mass index ($r=-0.456$, $P=.038$) (Table 3).

Table 3

Correlation analysis between lung ultrasound findings and other volume control parameters.

	r	P
Systolic blood pressure	0.172	.456
Diastolic blood pressure	0.355	.114
Body mass index	−0.214	.352
Cardiothoracic index	−0.217	.346
Pro BNP	−0.256	.263
VEGF	0.447	**.042**
Daily urine volume	0.582	**.007**
BIA	−0.094	.685
Left ventricular end systolic diameter	−0.288	.206
Interventricular septum thickness	−0.336	.137
Posterior wall thickness	−0.294	.195
Ejection fraction	0.131	.572
Left ventricle end systolic volume	0.028	.904
Left atrial volume	−0.123	.596
Left ventricle mass index	−0.456	**.038**
Left ventricle filling velocity	0.03	.896
E/E'	−0.136	.556
Pulmonary artery pressure	−0.315	.164
Left ventricle mass	−0.365	.104

BIA = bioelectrical impedance analysis, VEGF = vascular endothelial growth factor.

4. Discussion/conclusion

LUS in PD patients and its correlation with clinical, laboratory, radiologic volumetric parameters including physical examination, NT-proBNP, VEGF-C, chest radiography, echocardiography had been searched in this article. The number of B lines was correlated with daily urine volume, VEGF-C level, and LVMI. Dividing B lines into 2 groups from the median level has produced a significant difference in comparison of daily urine volume and VEGF-C level.

Physical examination focused on hypervolemia symptoms was normal except effort dyspnea and edema on a few patients. Stages of NYHA class, the presence of edema did not change LUS findings. Edema is not enough sense to determine volume status in dialysis patients.[17] A similar article comparing edema, NYHA class with LUS in PD population[16] had produced similar results like our study.

Panuccio et al[16] and Enia et al[18] have found no difference between daily urine output and LUS. There was a positive correlation between daily urine output and the number of B lines in our study. In addition, daily urine output of patients with the number of B lines>1 group was more than the other group. Echocardiographic findings of both groups were statistically similar excluding worse cardiac function as a possible cause of an increased number of B lines. Correlation of urine output with LUS findings may have 2 possible speculations. The first one is consumption of more liberal amounts of fluid by being aware of their increased urine output already. The other cause might be increased urine output as a response to hidden hypervolemia to prevent obvious congestion.

There is one report showing relationship VEGF-C levels with volume status in hemodialysis patients.[9] Highest VEGF-C levels were found in CKD patients at the predialysis stage with obvious hypervolemia. Its level was decreased after fluid removal in maintenance hemodialysis patient group. VEGF-C has never been used for the assessment of hypervolemia in PD before. Its level was positively correlated with the number of B lines and was significantly different when B lines were grouped. VEGF-C might be the surrogate marker reflecting a level of hidden hypervolemia in dialysis patients.

Paudel et al had grouped LUS findings into 3 according to the number of B lines and found a significant relationship with NT-

proBNP levels and LUS groups.[7] We have found that NT-proBNP levels were similar to each other in B line groups. There was no correlation between the 2 parameters as well.

There are 2 studies comparing BIA and LUS.[7,16] None of them have found a significant relationship between BIA and LUS as in our study.

Panucci et al had published the only study regarding echocardiography and LUS. They have found a significant difference between LUS findings and left atrial diameter, left atrial volume, left atrial volume/height and ejection fraction. We have not found any significant relationship between LUS groups and echocardiography parameters. The negative correlation between LVMI and number B lines has been found.

The main limitation of this study is a limited number of patients. Besides this, our study has several unique features. There are only a few studies evaluating the relationship of LUS and other parameters in adult PD population.[7,16,18] Paudel et al investigated the relationship between BIA and LUS;[7] Enia et al searched for comparison of quality of life and LUS;[18] Panuccio et al reported the correlation between echocardiography and LUS.[16] Our study has the widest spectrum of data including signs, symptoms, laboratory evaluation and radiological examination to compare with LUS findings. Moreover, we have found a significant correlation between VEGF-C and number of B lines which is a novel finding. Although VEGF-C level is not generally used in daily practice, this study may stimulate others to test the relationship between VEGF-C and hypervolemia.

LUS is practical and easy to perform tool that can be performed in PD patients to evaluate hidden hypervolemia. Its findings are not correlated with overt hypervolemia signs, symptoms and other classical methods of volume determination. Correlation of the number of B lines with serum VEGF-C levels needs to be further tested in a bigger patient population.

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