



Assessment of fluid status in chronic hemodialysis patients: Role of the doppler echocardiography and atrial natriuretic peptide

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ABSTRACT

Background: The evaluation of fluid status is generally approached from clinical observation of body weight changes, congestion, edema, blood pressure and chest X-ray. However, evaluation on clinical grounds alone is not accurate enough in HD patients; moreover, no single method has emerged as a gold standard to assess the fluid status in chronic hemodialysis patients.

Objectives: The aim of this study was to assess the fluid status among chronic hemodialysis patients using Doppler echocardiographic parameters including inferior vena cava diameter (IVCD) and its correlation to plasma atrial natriuretic peptide (ANP).

Patients and Methods: Sixty subjects were included in this study, 40 patients on chronic hemodialysis and 20 subjects as control group. The subjects of this study were classified into three groups; group 1, 20 normotensive patients who were on hemodialysis for at least six months; group 2, 20 hypertensive patients who were on hemodialysis for at least six months; and group 3, 20 healthy subjects without history of cardiac disease (as a control group). The IVCD was measured in all groups by ultrasound and Doppler echocardiography to estimate the pulmonary flow and post dialysis plasma atrial natriuretic peptide (ANP).

Results: A significant difference in the IVCD 2 hours after hemodialysis was seen between the hypertensive and the normotensive groups. In addition, we found that a significant difference in the peak pulmonary vein systolic velocity between the three groups. There was a significant negative correlation between the peak pulmonary systolic velocity to peak pulmonary diastolic and IVCD. In addition, there was a significant difference between mean ANP level among the three studied groups and the ANP was significantly correlated with IVCD in corresponding groups respectively.

Conclusions: The current study showed an increase in the IVCD and ANP as well as an increase S/D ratio in hemodialysis patients with hypertension than normotensive hemodialysis cases and the controls. Thus we emphasize the importance of assessment of fluid status using Doppler echocardiographic parameters as pulmonary venous flow using S/D ratio.

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► Implication for health policy/practice/research/medical education:

This article which describes fluid status in hemodialysis patients will be useful for practitioners who are active in the field of clinical nephrology and general practitioners.

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Background

Chronic renal failure (CRF) is a functional diagnosis characterized by progressive loss of all kidney functions (tubular and glomerular) with disturbance of the internal environ-

ment of the body. It is of gradual onset, progressive course and generally irreversible and ultimately ends by end-stage renal disease (ESRD) with its hard endpoints (dialysis, transplantation or death) (1). Terminal renal failure has an incidence of approximately 60 people per million populations, and is on the increase. Victims suffer from an appreciably compromised quality of life and life expectancy. The financial burden on the health service imposed by the need for renal replacement therapy is considerable (2). Plasma volume, in turn is determined by the total ECF volume and the par-

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tititioning of this volume between extra-vascular and intra-vascular compartments according to the dictates of the Starling relationship, also remains remarkably constant despite alterations in dietary salt intake. Uncontrolled hypertension during dialysis will lead to progression of left ventricular hypertrophy, which is a strong predictor for ischemic heart disease, cardiac failure, and death (3). The Framingham Heart Study and the Seventh Report of the Joint National Systolic Blood Pressure (SBP) often is volume dependent and associated with cardiovascular Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) noted an elevated SBP to be a more significant cardiovascular disease risk factor than diastolic blood pressure (4). Therefore, many have recommended focusing on controlling SBP, with target BP control recommended by the recent JNC guidelines (5). Blood pressure could be controlled in the majority of dialysis patients through the dry-weight method, noting that the absence of edema itself was not synonymous with reaching the dry weight (6). Natriuretic peptides are involved in the regulation of volume homeostasis. Their levels generally are increased in the setting of volume expansion and act on multiple effector systems to cause vasodilation and natriuresis in an effort to return volume status back to normal. In patients with end-stage renal disease, the natriuretic capabilities of these peptides are limited. However, there has been much interest in the potential applicability of measurement of these peptides as a surrogate marker of volume status and in the determination of dry weight. Furthermore, atrial natriuretic peptide and brain natriuretic peptide can serve as markers of left ventricular dysfunction and may have utility in determining cardiac prognosis in patients on long-term dialysis therapy (7). Circulating natriuretic peptides, particularly human atrial natriuretic peptide (ANP), regulate volume homeostasis and control BP and electrolyte balance (8). Sabrane K studied the pathophysiological mechanism of the extrarenal effects of ANP. And he suggested that the hypovolemic action of ANP is mediated by endothelial permeability changes of the GC-A gene (9).

Methods of estimation of fluid status in hemodialysis patients:

1. Measurement of jugular venous pressure
2. Absence of edema
3. Measurement of pre and post-dialysis blood pressure and weight
4. Ability to withstand ultrafiltration during dialysis
5. Biochemical markers
 - Atrial natriuretic peptide
 - Cyclic guanine monophosphate (cGMP)
6. Single dual frequency bio impedance analysis
7. Bioimpedance spectroscopy, the multi-frequency approach
8. Lung density for assessment of hydration status in hemodialysis patients
9. Doppler echocardiography:
 - Echocardiographic measurement of the inferior vena cava diameter
 - The mitral inflow Doppler spectrum reflects the left ventricle (LV) filling dynamics, and the pulmonary vein Doppler spectrum reflects the left atrium (LA) filling dynamics, respectively

Objectives

The aim of this study was to investigate the relationships between various Doppler echocardiographic data and ANP and other fluid status parameters in the assessment of fluid status among patients with chronic hemodialysis.

Patients and Methods

Sixty subjects were included in this study. Forty patients on chronic hemodialysis and twenty subjects were included as control group. They were selected from hemodialysis unit of Tanta university hospital, Internal medicine department. The subjects of this study were classified into three groups. *Group I:* Included 20 patients who had been on chronic hemodialysis 6 months at least and were normotensive without receiving anti-hypertensive agents.

Group II: Included 20 patients who had been on chronic hemodialysis 6 months at least and remained hypertensive under anti-hypertensive agents.

Group III: Included 20 subjects who are apparently normal without history of cardiac disease (as a control group).

Exclusion criteria

Subjects with mitral regurgitation of more than moderate severity, atrial fibrillation in rhythm, LV ejection fraction < 55% estimated by echocardiography. Subjects had technically inadequate Doppler recordings, with electrolyte disturbance and Subjects with pulmonary diseases. All the patients and control group were subjected to full clinical examination with special stress on blood pressure in standard conditions. We calculate the mean blood pressure (MBP) = diastolic blood pressure +1/3 pulse pressure (systolic blood pressure - diastolic Blood pressure) values were averages from 25 consecutive dialysis sessions after the echocardiographic study. Examination of extremities was done to exclude peripheral edema.

Hemodialysis procedure

The hemodialysis patients received a 4 hours dialysis session thrice weekly using 1.6 m² surface area dialysers with citrate based dialysate.

Laboratory investigations

- Blood urea, serum creatinine, Serum sodium, potassium, calcium, phosphorous and albumin.
- Complete blood count to exclude anemia, hemoconcentration, and hemodilution, plasma atrial natriuretic peptide by radioimmunoassay kits (Peninsula Laboratory Europe Ltd., St. Helens, Merseyside, UK) after pre-extraction by reverse chromatography (Seppak C-18 cartridges; Waters, Milford, MA, USA)
- ECG to exclude ischemic heart diseases and left ventricular hypertrophy
- Plain chest X-ray (Postero-anterior view) to exclude pulmonary diseases
- Ultrasound was performed before and after hemodialysis.
- Inferior vena cava sonography was performed in the supine position with 2-dimensional guide M-mode echocardiography, using a 3.75 MHz ultrasound probe. From a sub-xiphoidal long axis view, the diameters were measured immediately prior to the P-wave of the ECG, in end expiration. Valsalva like maneuvers were avoided. The sonography

which was performed after dialysis was done 2 hours after the end of the session.

Echocardiography

The Doppler spectrum of the mitral inflow was recorded between the tips of mitral leaflets in the four chambers view. The pulmonary vein Doppler spectrum was obtained; Echo Doppler spectra were analyzed with M-mode echocardiogram was recorded with simultaneous ECG monitoring. The IVC diameter was measured the use of the measuring software incorporated in the echo system. From the mitral inflow velocity tracings, peak velocity (E) and deceleration time (DT) of the early inflow wave, peak velocity (A) of the late inflow wave at atrial contraction, and isovolumic relaxation time (IVRT) were measured. The parameters evaluated for the pulmonary vein spectrum included the peak velocity of the systolic forward spectrum (S) and diastolic forward spectrum (D) in cases of a biphasic systolic pulmonary vein spectrum, the peak velocity was measured on the taller of the two peaks. The S/D ratio of the pulmonary vein spectrum was defined as the peak systolic velocity divided by the peak diastolic velocity; the E/A ratio of the mitral inflow spectrum was defined as the peak velocity of the early inflow wave divided by that of the late inflow wave.

Statistics

Statistical presentation and analysis of the present study was conducted, using the mean, standard error, Student t-test [Unpaired], paired t-test, analysis of variance [ANOVA] test, chi-square and correlation by SPSS V. 13.0.

Results

Basic patient's characters are shown in Table 1. There is no significance difference as regard age, height, pre dialysis body weight ($P > 0.05$). There is significant difference between group I, II, III ($91.85 \pm 5.72, 126.6 \pm 7.79$ and 89.75 ± 7.86) respectively as regard BDMBP ($P < 0.05$). There is significant difference between Na level in all group ($P < 0.05$), but no significance difference in K, Ca, and P ($P > 0.05$). Also there is significant difference in hematocrit value between group I, II ($43.3 \pm 3.42, 39.8 \pm 2.46$ and 48.2 ± 4.13) ($P < 0.05$) (Table 2). There was significance difference in MBP before and after dialysis in group I and II ($P < 0.05$). It is significantly difference in Na level and Hematocrit value in group II before and after dialysis ($P < 0.05$).

Table 3 show significance difference between studied groups as regard IVCD pre and post dialysis also peak pulmonary vein systolic velocity (S) and diastolic velocity (D) and its ratio ($P > 0.05$). No significant difference between studied group as regard peak early mitral inflow velocity (E) and also peak late mitral inflow velocity (A) but E/A ratio is significantly different ($P < 0.05$). No significant difference as regard Deceleration Time of early mitral inflow (DT) ms and Isovolumic Relaxation Time (IVRT) ms. Atrial natriuretic peptide was measured in post-hemodialysis in euvolemic patients there was significance difference between group I (57.4 ± 4.42) and group II (137.8 ± 22.7) as regard ($P < 0.05$). When post-HD ANP was between 40 and 60pg/mL the possibility that the DW is appropriate was as high as 95.8%. In contrast, when post-HD ANP was over 100 pg/mL or below 25 pg/mL, the potential for DW to be appropriate was as low as 42.9% and 29.2%, respectively.

Table 1. Comparison between the studied groups as regards basic patient's characters and investigation

	Group I	Group II	Group III	p-value ^c
Age (Mean \pm SD)	36.45 \pm 9.32	36.45 \pm 7.97	32.25 \pm 7.68	0.19
Height (Mean \pm SD)	165.75 \pm 8.4	157.1 \pm 14.11	159.6 \pm 13.12	0.07
PDBW ^a (Mean \pm SD)	69.2 \pm 8.46	68.3 \pm 8.55	68 \pm 6.53	0.88
BDMBP ^b (Mean \pm SD)	91.85 \pm 5.72	126.6 \pm 7.79	89.75 \pm 7.86	0.000
Na ⁺ (Mean \pm SD)	138.65 \pm 5.84	129.35 \pm 7.07	138.65 \pm 3.56	0.000
K ⁺ (Mean \pm SD)	4.5 \pm 0.58	4.54 \pm 0.72	4.31 \pm 0.49	0.44
Ca ⁺ (Mean \pm SD)	8.44 \pm 0.76	8.74 \pm 0.84	8.8 \pm 0.61	0.26
P ⁻ (Mean \pm SD)	5.13 \pm 0.48	4.94 \pm 0.62	4.82 \pm 0.3	0.14
Hematocrit (Mean \pm SD)	43.3 \pm 3.42	39.8 \pm 2.46	48.2 \pm 4.13	0.000
Albumin (Mean \pm SD)	3.91 \pm 0.36	3.79 \pm 0.462	4.19 \pm 0.29	0.006

^a PDBW: pre-dialysis body weight

^b BDMBP: before dialysis mean blood pressure

^c Significant ($P < 0.01$).

Table 2. Comparison between studied groups as regard MBP, Na and Hematocrite before and after dialysis

	MBP in pre and post dialysis mmHg		Serum (Na ⁺) in pre and post dialysis		Hematocrit values in pre and post dialysis	
	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Group I						
Before	91.85 ± 5.715	0.000 ^a	138.65 ± 5.84	0.41	43.3 ± 3.42	0.30
After	85.8 ± 5.197		139.45 ± 5.28		43.6 ± 3.86	
Group II						
Before	126.6 ± 7.789	0.000 ^a	129.35 ± 7.1	0.000 ^a	39.8 ± 2.46	0.000 ^a
After	115 ± 6.689		134.78 ± 7.33		43.6 ± 2.23	

^a Significant (p < 0.01).

Table 3. Comparison between studied group as regard methods of detection of body fluid before and after dialysis

	Group I	Group II	Group III	p-value ^a
Pre dialysis U/S diameter of the IVCD (cm) (Mean ± SD)	1.47 ± 0.142	1.83 ± 0.195	1.23 ± 0.142	0.000
Post dialysis U/S diameter of the IVCD (cm) (Mean ± SD)	1.36 ± 0.135	1.585 ± 0.173	-	0.000
peak pulmonary vein systolic velocity (S) (Cm/s) (Mean ± SD)	71 ± 5.31	63.3 ± 7.328	73.95 ± 5.652	0.000
peak pulmonary vein diastolic velocity (D) (Cm/s) (Mean ± SD)	37.9 ± 3.076	56.85 ± 6.268	53.5 ± 6.203	0.000
S/D ratio	1.886 ± 0.214	1.123 ± 0.169	1.774 ± 0.216	0.000
Peak early mitral inflow velocity (E) (Cm/s) (Mean ± SD)	80.325 ± 6.74	83.1 ± 4.494	80.4 ± 4.903	0.19
peak late mitral inflow velocity (A) (Cm/s) (Mean ± SD)	81.5 ± 5.634	78.6 ± 4.147	81.9 ± 4.756	0.07
E/A ratio (Mean ± SD)	0.991 ± 0.117	1.058 ± 0.035	0.984 ± 0.074	0.01
Deceleration Time of early mitral inflow (DT) (ms) (Mean ± SD)	224 ± 26.76	216.95 ± 25.78	210.8 ± 23.63	0.26
Isovolumic Relaxation Time (IVRT) (ms) (Mean ± SD)	130.8 ± 24.296	123.1 ± 11.525	122.4 ± 7.287	0.19
Post dialysis atrial natriuretic peptide (pg/mL) (Mean ± SD)	57.4 ± 4.42	137.8 ± 22.7	55 ± 5.98	0.001

^a Significant (P < 0.01).

Table 4 and Figures 1 & 2 showed the correlation between S/D, BDMBP and IVCD in group II. There were significant correlation between S/D, BDMBP and P < 0.001, r = - 0.79. Also there were significant correlation between S/D, and IVCD P < 0.001, r = - 0.88. Table 4 and Figures 3 & 4 showed the correlation between E/A, BDMBP and IVCD in group II. There were no significant correlation between E/D, BDMBP and p-value = 0.65, r = -0.105. Also there were no significant correlation between

S/D, and IVCD p-value = 0.52, r = - 0.15. There is significant correlation between IVCD and ANP r = 0.788 P < 0.001.

Discussion

Terminal renal failure has an incidence of approximately 60 people per million populations, and is on the increase. The financial burden on the health service imposed by the need for renal replacement therapy is considerable (2). Hypertension is seen in the majority of patients with end-stage renal disease (ESRD) on hemodialysis, occurring in more than 70% of the patients in the large multicenter Hemodialysis (HEMO) Study (10). It is well accepted that hypertension can be controlled by adequate dialysis and the maintenance of dry weight in 85% to 90% of dialysis patients. In one center in Tassin, France, almost 98% of the patients were normotensive while receiving no medication by long and slow dialysis (11). Echocardiography is a well-established non-invasive

Table 4. Correlation between S/D, E/A, BDMBP and IVCD in group II

	S/D ^a		E/A ^b		ANP	
	r	p-value	r	p-value	r	p-value
BDMBP	- 0.795	< 0.001 ^c	- 0.105	0.659	-	-
IVCD	- 0.880	< 0.001 ^c	0.150	0.528	0.788	< 0.001 ^c

^a Systolic velocity (s) and Diastolic velocity (D) ratio

^b Early mitral inflow velocity (E) and Late mitral inflow velocity ratio

^c Significant (P < 0.01)

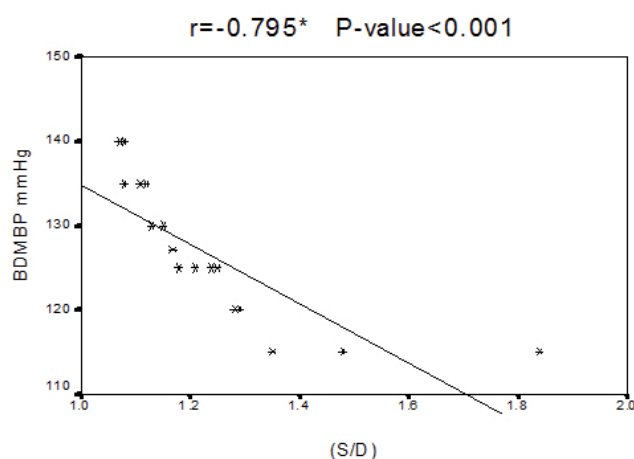


Figure 1. Correlation between S/D, BDMBP in group II

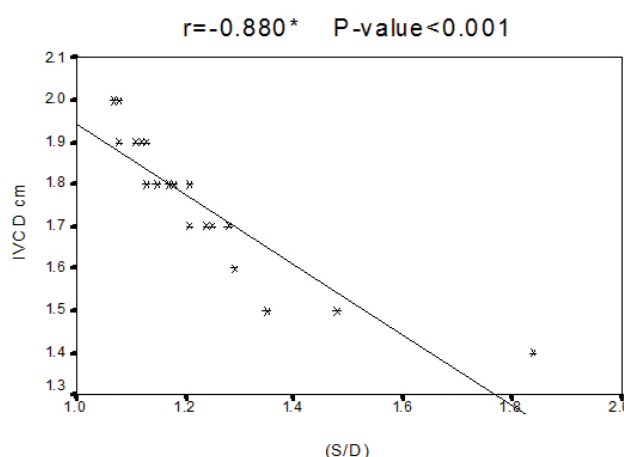


Figure 2. Correlation between S/D, IVCD in group II

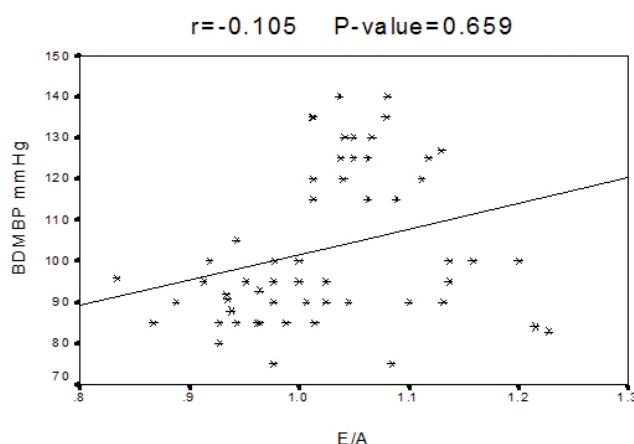


Figure 3. Correlation between E/A, BDMBP in group II

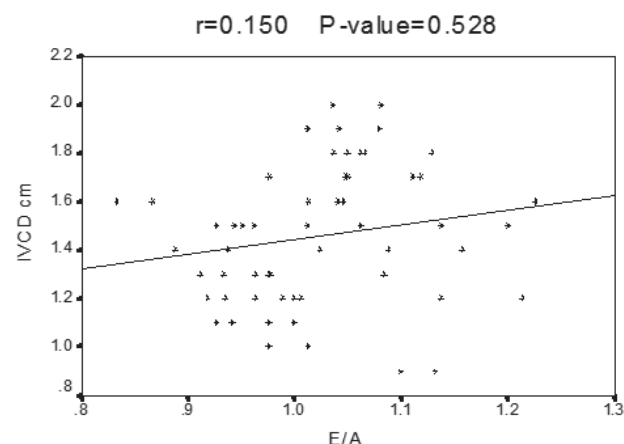


Figure 4. Correlation between E/A, IVCD in group II

technique to assess cardiac dimensions, volumes, and wall thickness, mass and dynamic function in an accurate and reproducible fashion (12). The mitral inflow Doppler spectrum reflects the left ventricle (LV) filling dynamics, and the pulmonary vein Doppler spectrum reflects the left atrium (LA) filling dynamics respectively. In consequence, the mitral inflow and pulmonary vein Doppler spectra may have the potential to complement the present methods of fluid status assessment (13). The present study comprehensively investigated the potential of the application Doppler echocardiographic parameters in the evaluation of the fluid status in HD patients. The major findings of the present study were:

I. The pulmonary vein and mitral Doppler echocardiographic parameters were significantly different between the HD patients and normal controls.

II. The pulmonary vein and mitral Doppler echocardiographic parameters were significantly different between HD patients who had and had not attained dry weight.

III. The S/D ratio from the pulmonary vein Doppler spectrum is a potentially useful marker for assessing fluid status in HD patients (14).

As regard the pulmonary venous flow spectra fluid status is increasingly believed to be an important determinant of blood pressure in HD patients. Volume expansion is significantly correlated to casual (BDMBP) and 24-h arterial pressure, and the normalization of the patient hydration status is followed by a reduction in pressure values. We are agreed with (15). As in our study we found that S/D ratio significantly lower in hypertensive group and were negatively correlated

with Before Dialysis Mean Blood Pressure (BDMBP). As regard IVCD we found that there was a negative correlation between S/D ratio and the IVCD as S/D ratio decreased before hemodialysis while IVCD significantly increased before hemodialysis in hypertensive patients. In agreement with our study, ERIC H Y (16) show that The systolic to diastolic (S/D) ratio of peak PV flow velocity after HD (2.15; 1.08 to 3.90) was significantly higher ($p < 0.01$) than before HD (1.80; 1.25 to 2.68), and was negatively correlated with IVCD which was 11.6 ,8.8 mm/m² before and after hemodialysis respectively. On the other hand, ERIC H Y, *et al.* (16) disagreed with us as they used Inferior Vena Cava Index (IVCI) while we used IVCD in our study. As regard mitral inflow velocity spectra E/A ratio was significantly higher in hypertensive group on chronic hemodialysis than normotensive group on chronic hemodialysis and normal control group but E/A ratio was not correlated with (BDMBP) nor (IVCD) in hypertensive group. In disagreement with us, Chih-Cheng Wu (17) show that E/A ratio in hypertensive hemodialysis patients was correlated well with BDMBP. Also disagreed with us as it showed that E/A ratio increased before hemodialysis and decreased after hemodialysis in hypertensive patients on chronic hemodialysis and was correlated with the IVCD.

As regard Deceleration Time of early mitral inflow velocity (DT) and Isovolumetric Relaxation Time (IVRT) there was no significant difference between hypertensive group, normotensive group and control group, Chih-Cheng Wu (17), As regard inferior vena cava diameter measurement by ultrasonography before and after hemodialysis our results

agreed with the study done by Leunissen *et al.* (18). They considered that the IVCD is related to the body surface area being 8-11.5mm/m² of body surface area. While another study done by Mandelbaum and Ritz (19), which included a group of 86 healthy control (43 male and 43 female), they found that the normal range was (13-28mm) with a mean value of 20 mm, and the IVCD was not correlated to age, height, weight or body surface area. So in our study we did not measure the IVCD by using the surface area of the body because it is affected by the body weight and height and were not correlated in normal to IVCD in the study of Mandelbaum and Ritz (19). Leunissen *et al.* (18), have used collapsibility index (maximal diameter on deep expiration minus minimal diameter on deep inspiration divided by maximal diameter on deep expiration) by 100, while Mandelbaum and Ritz (19) have found that the collapsibility index was less reducible, therefore, they abandoned the collapsibility index and only used the diameter for analysis. As regards the inferior vena cava diameter at the end of inspiration George Metry *et al.* (20) reported that it was markedly dilated after hemodialysis in severely over hydrated patients, which could be possibly, be due to poor inspiratory collapse. Also inferior vena cava diameter at maximum inspiration greatly decreased in normally hydrated and anhydrate patients after hemodialysis. Thus the inferior vena cava diameter at maximum inspiration did not properly reflect the changes in fluid status hence dry weight with hemodialysis George Metry *et al.* (20). In our study, the mean value of IVCD before and after hemodialysis had a highly significant difference. This is in agreement with Katzarski *et al.* (21), and also with Mandelbaum and Ritz (20). These results showed that the S/D ratio from the pulmonary vein Doppler spectrum is a potentially useful marker for the fluid status in HD patients as compared to other methods. Our data showed significance difference between normotensive and hypertensive patients post-dialysis as regard ANP, our results in agreement with Um HJ *et al.* (22) so that plasma values of ANP might be helpful clinical markers for evaluating volume status and assessing dry weight in maintenance hemodialysis patients. Also our results were in agreement with Wallin *et al.* (23) as they found that Natriuretic peptides are released by the heart in response to derangements in blood pressure and extracellular volume so there is high correlation between plasma ANP levels and cardiac output in patients on dialysis. The target range for post-HD ANP is 40-60 pg/mL to attain an appropriate dry body weight in chronic hemodialysis patients (24).

Conclusion

ANP & S/D ratio can be used as a good tool to assess the fluid status in chronic hemodialysis patients to adjust their dry weight to avoid volume overload hence hypertension due to increased cardiac output. ANP was a good indicator for body fluid status; S/D ratio can be used as a good tool to assess the fluid status in chronic hemodialysis patients specially if combined with others as inferior vena cava diameter (IVCD), chest X-ray, hematocrit value, serum sodium and serum albumin before and after hemodialysis.

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Conflict of interest

None declared.

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