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RESEARCH ARTICLE

The Role of Arteriovenous Shunt on Increased Prevalence of Unexplained Pulmonary Hypertension in Hemodialysis Patients .

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Abstract

Background: recent studies have shown a high incidence of unexplained pulmonary hypertension (PHT) in end-stage renal disease (ESRD) patients with or without haemodialysis (HD) therapy. The aim of this study was to evaluate the prevalence of unexplained PHT among patients with ESRD on regular HD and possible role of arteriovenous (AV) shunt as an etiological factor.

Materials and methods: We enrolled 80 consecutive patients with ESRD on regular HD via AV shunt. Forty random chronic kidney disease (CKD) (predialysis) patients were taken up as a control. All patients underwent transthoracic echocardiography to assess the pulmonary artery pressure and cardiac output (CO). Pulmonary hypertension was defined as, pulmonary artery systolic pressure (PASP) greater than 35 mm Hg at rest. In HD patients with PHT, we reassessed CO and PASP before and after 1 minute of temporary compression over the AV shunt.

Results: Patients on HD had higher PASP in comparison to control group. Out of 80 HD patients studied, 16 patients (20%) had PHT (PASP = 46±2 mmHg) while the rest had a normal PASP (29±1 mmHg) ($P<0.0001$). HD patients with PHT had significantly longer duration of dialysis ($P<0.001$), Higher CO in comparison to patients with no PHT ($P<0.05$). During AV shunt compression, the mean CO significantly decreased from (9.256±1.7538) L/min to (7.775±1.7842) L/min ($P<0.001$) and the mean PASP significantly decreased from (59.1644±17.28545) mmHg to (49.6300±14.91912) mmHg ($P<0.001$).

Conclusion: Our study demonstrated a high prevalence of PHT among patients with ESRD receiving long-term HD with surgical AV shunt. Both ESRD and long-term HD may be involved in the pathogenesis of PHT by affecting pulmonary vascular resistance and CO. Pathological elevation of PAP occurs in those patients whose pulmonary circulation cannot compensate for AV access-related high CO. This unrecognized complication of HD therapy is not uncommon.

INTRODUCTION

Cardiovascular complications are major causes of mortality in patients with chronic renal failure (CRF) receiving regular hemodialysis (HD)**.**[(1)] The prevalence of PHT in end-stage renal disease (ESRD) patients on HD has been documented to be 29-52 %.[(2)] Pulmonary arterial pressure (PAP) may be further increased by high cardiac output (CO) resulting from the arterio-venous (AV) access itself, worsened by commonly occurring anemia and fluid

overload.[3] It appears that patients with ESRD acquire endothelial dysfunction that reduces the ability of their pulmonary vessels to accommodate the access mediated elevated CO, exacerbating the PHT.[3] The vascular access formed for HD therapy is artificial often causing a large left to right shunt whose capacity often increases with time. Currently, there are no standard criteria regarding optimal AV access size.[4] ***Yigla et al*** suggested in their comprehensive studies that pathologic elevation of PAP occurs in patients whose pulmonary circulation cannot compensate for the AV access-related high CO. They recommended that surgical reduction of oversized AV access should be considered in patients with PHT and extremely high CO who demonstrate reduction of both CO and PHT following temporary closure of their AV access.[3] The aim of this study was to evaluate the prevalence of unexplained pulmonary hypertension among patients with ESRD on regular HD and possible role of AV shunt as an etiological factor.

2. Materials & methods:

2.1. Study population:

This study was conducted at the hospitals affiliated to the Benha University between May 2014 and January 2015. We prospectively enrolled 80 patients with ESRD who are on regular HD via AV shunt regardless to duration of dialysis. ESRD was defined as serum creatinine concentration four or more times higher than normal for age and gender, or a glomerular filtration rate (GFR) below 15 ml/ min per 1.73m2 for at least three months.[5]

Forty chronic kidney disease (CKD) patients on conservative management (pre dialysis) were taken up as a control group. CKD was defined as creatinine concentration two or more times higher than normal for age and gender, or as a GFR below 30 ml/min/1.73m^2 for at least three months.[5]

2.2. Exclusion Criteria:

Patients with known etiology or clinical condition that predispose to pulmonary hypertension such as parenchymal lung disease, previous pulmonary embolism , collagen vascular disease and cardiac diseases such as left ventricular systolic dysfunction , advanced LV diastolic dysfunction ≥ grade III, left-to-right shunt and significant mitral or aortic valve disease.

Patients with PHT (defined as PASP>35mmHg) were evaluated further by an experienced pulmonologist in order to uncover other potential causes of PHT. This assessment included other advanced investigations when needed as chest CT, complete pulmonary function tests, measurement of arterial blood gases and oxygen saturation, ESR and antinuclear antibodies (ANA).

2.3. Methods:

The following data were collected:

2.3.1 History and clinical evaluation:

- The patient's general data (age, sex, co morbidities) plus general and local cardiac examination.
- Data regarding the kidney disease as duration of HD therapy and access location [brachial or radial].

2.3.2 Investigations:

- Standard 12 leads surface ECG.
- Chest X ray P-A view.
- Lab. work: Hemoglobin (Hb) %, serum creatinine & blood urea.

2.3.2.1 Echocardiography:

A complete 2D, M mode and Doppler echocardiographic study was obtained on each patient within 1 hour after completion of dialysis to avoid overestimation of PAP due to volume overload. Cardiac output is obtained by multiplying stroke volume by heart rate.

Stroke volume (SV) was calculated by multiplying time velocity integral (TVI) by cross section area (CSA):
SV = CSA x TVI

Measurement of LVOT velocity and time velocity integral (TVI) was obtained from the apical long-axis view. A pulsed wave sample volume was placed at the center of the aortic annulus or 2-5 mm proximal. TVI (cm) was defined as the area under the velocity curve and equal to the sum of velocities (cm/sec) during the ejection time (sec).
CSA = $(D / 2)^2 \times \pi = D^2 \times 0.785$ where D is LVOT diameter. [6]

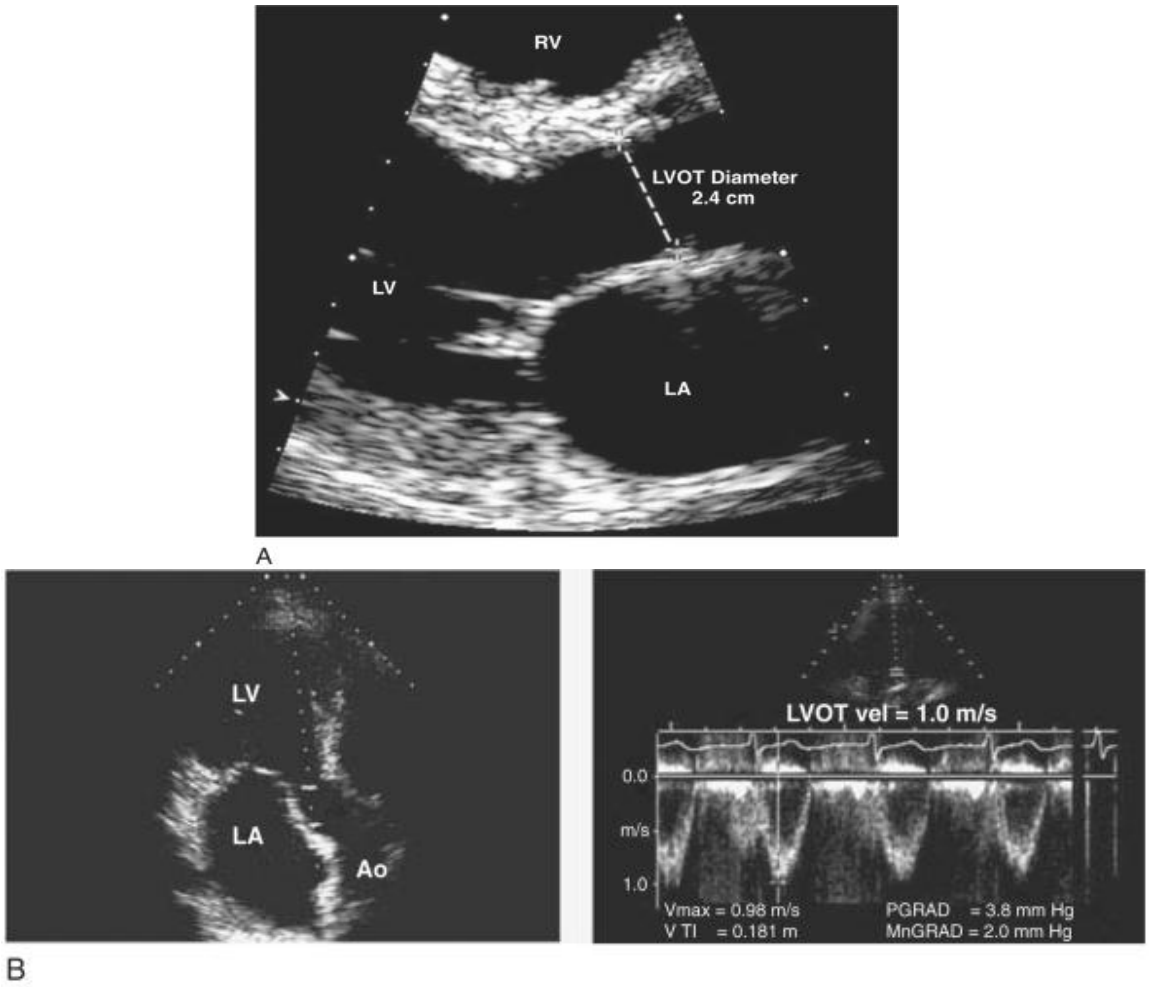

Figure 1: calculation of stroke volume from the left ventricular outflow tract. [7]

- Pulmonary artery pressure was calculated, In the presence of tricuspid regurgitation (TR), using Continuous wave Doppler echocardiography to estimate the systolic PAP. Systolic right ventricular (or pulmonary artery) pressure were calculated using the modified Bernoulli equation: PAP = 4 x (tricuspid regurge peak velocity m/sec.) ^{2} + the right atrial pressure. Right atrial pressure was estimated with 2-D mapping in the sub costal window using IVC diameter with its respiratory variation (normal IVC diameter is under 1.5 cm with normal inspiratory collapse more than 50%).[8]

- In presence of PHT, we reassessed CO and PASP following temporary compression of the AV shunt using cuff of sphygmomanometer and raising pressure until absence of peripheral pulsation.
- Pulmonary hypertension has been defined as a systolic pulmonary artery pressure> 35mmHg (mild up to 49 mmHg, moderate 50-69 mmHg, severe≥ 70 mmHg). [9]
- LVH is present if septum and posterior wall thickness ≥ 13mm by M mode in Echo Doppler study. [10]
- Diastolic dysfunction assessed using Doppler diastolic indexes of transmitral E/A ratio < 1 (pattern of abnormal relaxation), 1-2 (pseudonormalization, differentiated from normal by repeating measurement during Valsalva

maneuver or after administration of nitroglycerine reverted to abnormal relaxation pattern while truly normal had a reduction in both E and A velocities but the E/A ratio had no change) and > 2 (restrictive patterns)**.** [(11)]

All procedures were performed in accordance with the ethical standards of Benha University.

2.4. Statistical analysis:

All statistical analysis was performed using the SPSS 17.0 software. Values were expressed as mean ± Standard deviation (SD) and as percentage for categorical parameters.

3. Results:

We found no significant differences in demographic and clinical characteristics between patients on HD and control group. But as expected, they had higher serum creatinine, CO and EF than controls. Also they had a non significant higher PASP in comparison to control group (P>0.05).

Out of 80 HD patients studied, 16 patients (20%) had PHT (PAP = 46±2; range 36-82 mmHg) while the rest had a normal PAP (29±1 mmHg) (P<0.0001).

There were no significant differences between HD patients with and without PHT as regard age, sex, DM, HTN , shunt site ,HR, systolic BP and diastolic BP. However, HD patients with PHT had significantly longer duration of dialysis (70.88 months vs 22.34 months) (P< 0.001) **(Table 1).**

Table 1: Demographic and clinical characteristics in HD patients with and without PHT.

variables	HD patients with PHT	HD patients without PHT	P value
No. of patients	16	64	
Age(y) (Mean±SD)	51.06±6.567	50.98±12.234	>0.05
Gender (male/female)	12(75%)/4(25%)	52(81.2%)/12(18.8%)	>0.05
DM	7 (43.8%)	17 (26.6%)	>0.05
HTN	11 (68.8%)	39 (60.9%)	>0.05
Dialysis Duration (months)	70.88±27.208	22.34±30.618	<0.001
Shunt Site(Brachial/Radial)	5(31.3%)/11(68.7%)	10(15.6%)/54(84.4%)	>0.05
HR(BPM)	91.06±10.08	89.69±8.602	>0.05
Systolic BP(mmHg)	135.00±18.974	129.77±16.389	>0.05
Diastolic BP(mmHg)	84.06±12.678	77.89±12.012	>0.05

Echocardiographic data revealed that HD patients with PHT had significantly higher mean CO (9.256 L/min vs 8.192 L/min) (P<0.05). Also they had significantly higher mean PASP (59.1644 mmHg vs 26.6255 mmHg)

(P<0.001) while no significant differences were found as regard EF%. **(Table 2)** As regard other echocardiographic data as LVH and LV diastolic dysfunction, there were no statistically significant differences.

Table 2: Echocardiographic data in HD patients .

variables	HD patients with PHT	HD patients without PHT	P value
Mean CO	9.256 L/min	8.192 L/min	<0.05
Mean PASP	59.1644 mmHg	26.6255 mmHg	<0.001
EF%	61.69%	63.91%	>0.05

As regard the effect of temporary shunt compression on CO and PASP in HD patients with PHT , the mean CO decreased from (9.256±1.7538) L/min to (7.775±1.7842) L/min with highly significant difference (P<0.001). **(Figure 2)** and the mean PASP decreased from (59.1644±17.28545) mmHg to (49.6300±14.91912) mmHg with also highly significant difference (P<0.001). **(Figure 3)**

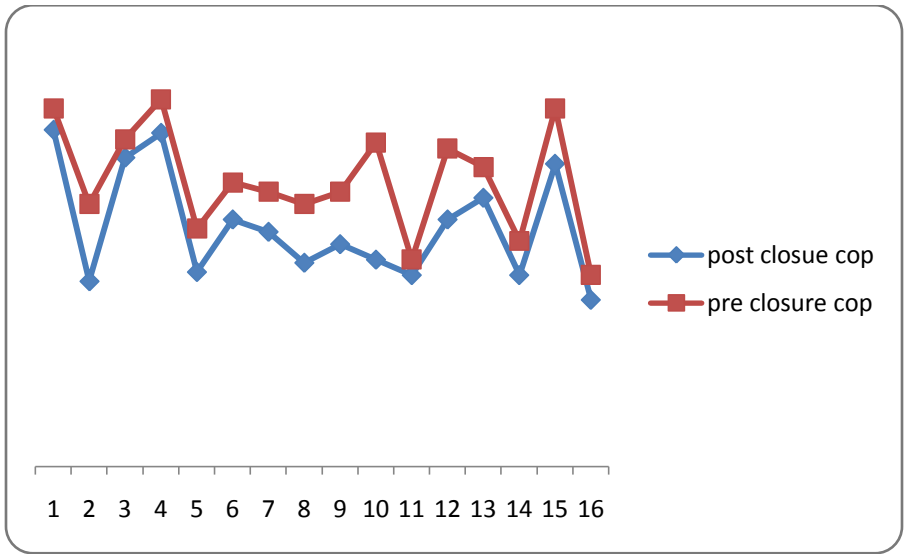

Figure 2: Effect of temporary AV shunt compression on CO.

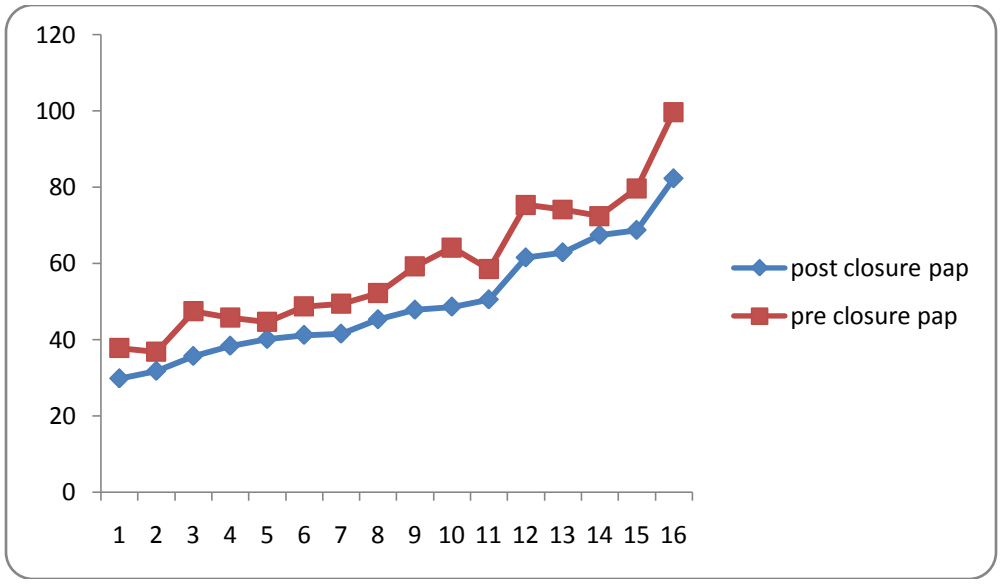

Figure 3: Effect of temporary AV shunt compression on systolic PAP.

Among 16 patients on HD with PHT, the correlation between systolic PAP and CO was investigated and positive relationship was found between them (r=0.257 and P=0.005). **(Figure 4)**

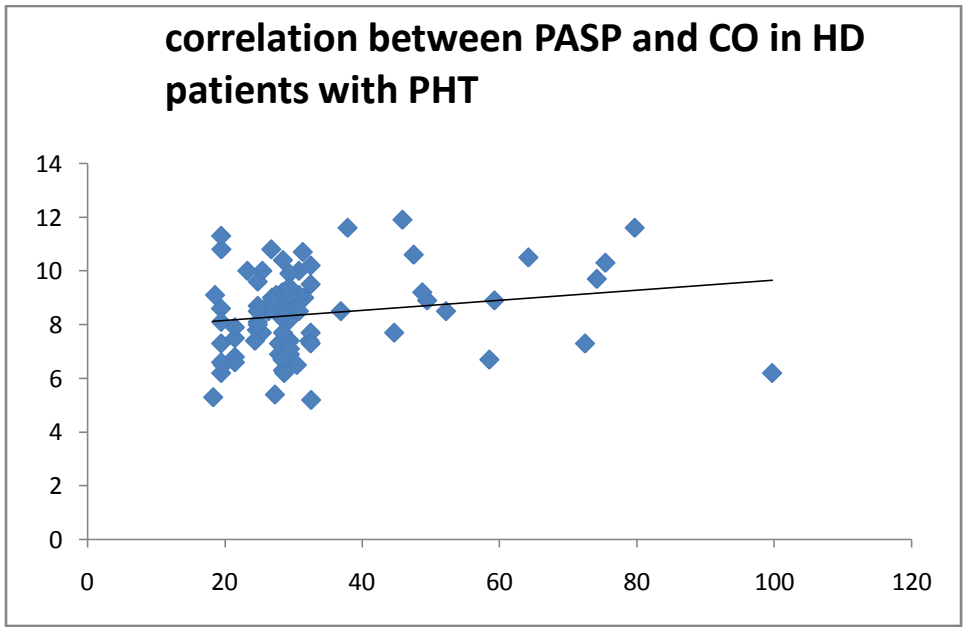

Figure 4: correlation between systolic PASP and CO in HD patients with PHT

Univariate analysis for PHT with different variables showed that dialysis duration (months), Hb% (gm/dl) and CO (L/min) were the significant variables (predictors).
Multivariate regression analysis for PHT with different variables showed that dialysis duration (months) is the only significant variable (independent factor contributing to PHT) (B = 0.527, P =0.037) **(Figure 5).**

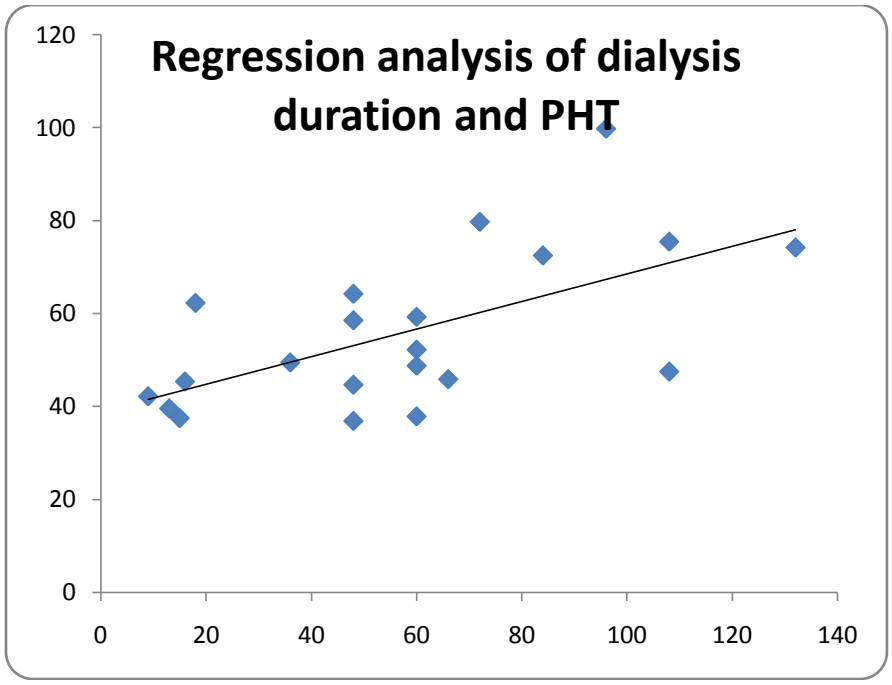

Figure 5: Regression analysis of dialysis duration and PHT

4. Discussion:

There were many medical complications reported in patients with CRF. One of the uncommonly reported complications of CRF is PHT. The pathogenesis of PHT in patients with CRF has not been explained satisfactorily. [12, 13] During the last 4 decades, patients with ESRD maintain life with the aid of HD via surgical AV access. The impact of AV shunt on the pulmonary circulation has not been studied adequately. [4] Temporary AV access closure and successful kidney transplantation causes a significant fall in CO and PAP, indicating the possibility that excessive pulmonary blood flow is involved in the pathogenesis of the disease.[14]

4.1. Major findings:

Our study demonstrated a high prevalence of PHT among patients with ESRD receiving long-term HD with surgical AV shunt (20%). Nearly similar prevalence was found by ***Canan et al, Tarrass et al. and Amin et al.*** [15, 16, 17] who stated that PHT was found in (21.6%, 26.74% and 29%) in patients on HD via AV access. Higher prevalence was reported by ***Yigla et al., Abdelwhab et al, Nakhoul et al. and Mazdeh et al*** [4, 18, 19, 20] who found PHT in (39.7%, 44.4%, 48% and 51.6%) of ESRD patients on regular HD. This higher prevalence may be attributed to different methodology used as they performed doppler echocardiogram on the day post dialysis leading to increase volume overload.

In contrary to our study, ***Haris et al***. [21] had a study to assess the prevalence of PHT in patients with ESRD on HD as measured by right heart catheterization and comparing them with patients who have chronic kidney disease (CKD) as well as patients with normal GFR. Prevalence of PHT in patients with CKD or ESRD didn't differ significantly from patients with normal GFR. This may be attributed to using right heart catheterizations in evaluation of PAP and defining PHT as a mean pulmonary artery pressure of greater than 25mmHg.[21]

We compared different demographic, clinical, hemodynamic, and metabolic variables among HD patients with and without PHT. Patients with PHT had significantly higher CO, lower HB, and experienced a longer duration of HD therapy ($P<0.001$) **(Table 1).** This is comparable with ***Anna et al. and Nasri et al*** [2, 22] who reported that PHT patients were more likely to have extended HD durations.

The mean CO was significantly higher in HD patients with PHT ($P<0.05$) while no significant differences were found between both groups as regard to EF%, LVH and diastolic dysfunction **(Table 2).** This is comparable with ***Yigla et al and Nakhoul et al***. [4, 19] who found that patients with PHT receiving HD had a significantly higher CO.

The correlation between PASP and CO in HD patients was investigated in our study and positive relationship was found between them (r=0.257 and P=0.005) **(Figure 4).**

Although anemia is associated with a compensatory increased CO, the more pronounced anemia in the patients with PHT does not explain all the differences in the CO. It appears that other factors, such as the size (or the amount of blood shunted) of AV access, are involved in the mechanism that increases CO.

4.2. CO and PASP following temporary compression of the AV shunt:

During this maneuver, the mean CO decreased from (9.256±1.7538) L/min to (7.775±1.7842) L/min with highly significant difference (P<0.001). The mean PASP decreased from (59.1644±17.28545) mm Hg to (49.6300±14.91912) mm Hg with highly significant difference (P<0.001) **(Figures 2 & 3).** This is comparable with ***Nakhoul et al.***[19] who found that temporary closure of the AV access by a sphygmomanometer in eight patients with PHT resulted in a transient decrease in CO (from 6.4±0.6 to 5.3± 0.5 l/min, P = 0.18) and PASP (from 47.2±3.8 to 34.6±2.8 mmHg (P<0.028). Also ***Clarkson et al***.[23] reported that surgical ligation of the AV fistula and insertion of a semi-permanent internal jugular dialysis catheter reduced the PAP from 60 mmHg to 30 mmHg.

4.3. Univariate & Multivariate regression analyses for PHT with different variables:

Univariate analysis for PHT with different variables showed that dialysis duration (months), Hb% (gm/dl) and CO (L/min) were the significant variables (predictors).

Multivariate regression analysis for PHT with different variables showed that dialysis duration (months) is the only significant variable (independent factor contributing to PHT) (B = 0.527, P =0.037). This is may reflect the role of both hemodialysis and AV shunt in development of PHT in ESRD **(Figure 5).**

4.4. Potential limitations of this study should be addressed:

The exclusion criteria used in our protocol resulted in a small study group. PAP was noninvasively measured by doppler echocardiography without obtaining direct invasive measurements. However, measurements of PAP by the applied doppler echocardiographic method were reported to have an excellent correlation with measurements obtained by invasive methods.[24]

5. Conclusion:

Our study demonstrated a high prevalence of PHT among patients with ESRD receiving long-term HD with surgical AV shunt. Both ESRD and long-term HD may be involved in the pathogenesis of PHT by affecting pulmonary vascular resistance and CO. Pathological elevation of PAP occurs in those patients whose pulmonary circulation cannot compensate for AV access-related high CO. Furthermore, the partial restoration of normal PAP and CO in patients that underwent temporary AV shunt compression indicates that excessive pulmonary blood flow is involved in the pathogenesis of the disease. This unrecognized complication of HD therapy is not uncommon.

Conflict of interest:

The authors declare no conflict of interests.

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