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AN ECHOCARDIOGRAPHIC EVALUATION OF PULMONARY PRESSURES IN HEMODIALYSIS PATIENTS AT KENYATTA NATIONAL HOSPITAL, NAIROBI, KENYA

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ABSTRACT

Background: **A high prevalence of pulmonary hypertension (PH) in patients with end-stage renal disease (ESRD) has been noted. In these patients, PH increases morbidity and mortality and worsens prognosis post-renal transplant. Its aetiopathogenesis may be multifactorial, involving the process of haemodialysis itself.**

Objective**: To determine the prevalence of PH among patients with ESRD undergoing haemodialysis at Kenyatta National Hospital (KNH), using Doppler echocardiography**

Design: **117 patients were consecutively recruited into this cross-sectional study. Medical history was used to exclude patients with possible PH of known aetiology. Patients were examined for features of fluid overload. Each patient then underwent haemodialysis followed by echocardiography within two hours. Haemoglobin was measured.**

Setting**: The Renal Unit, KNH, a tertiary hospital in Nairobi**

Subjects: **Patients undergoing regular haemodialysis within the renal unit, thirteen years and above, who gave written informed consent or assent.**

Results: **63.2% of the participants were male. Mean age was 44 years. Prevalence of PH among ESRD patients was 32.5%, with a median PASP of 47.3mmHg and a range of 36.1–79 mmHg. A strong association between PH and EF of less than 50%, as a marker of LV dysfunction, was demonstrated.**

Conclusion**: The prevalence of PH among end-stage renal disease patients was high. This suggests an indication for routinely screening haemodialysis patients for PH.**

Key Words

ESRD End stage renal disease
LV Left ventricle
KNH Kenyatta National Hospital
PASP Pulmonary arterial systolic pressure
PH Pulmonary Hypertension

BACKGROUND

Increased use of Doppler echocardiography for the assessment of pulmonary hypertension (PH) has shown that PH is much more common than traditionally had been thought [1,2]. Several recent studies [1,2] have also revealed pulmonary pressures to be elevated in patients with end-stage renal disease (ESRD) on haemodialysis (HD). In ESRD, PH increases morbidity and mortality [1] and is an independent risk factor for death []. Further, prognosis is worse in post-transplant patients with PH [2] and even renal transplantation may not reverse the high mortality conferred by PH [2]. Prospective data regarding the prevalence of PH in ESRD and its clinical determinants is limited and in Sub- Saharan Africa, no studies have been undertaken. Table 1 summarizes some of the studies investigating the prevalence of PH in patients on HD.

Pulmonary Hypertension is defined as a mean pulmonary arterial pressure (mPAP) of more than 25 mmHg, as measured through right heart catheterization (RHC), with the patient at rest [2**].** Doppler echocardiography estimates have been shown to be closely correlated to that measured via RHC [2]. Doppler estimates measure pulmonary artery systolic pressure (PASP) as a representation of right ventricular systolic pressure, in the absence of right ventricular outflow obstruction. PASP is estimated by the modified Bernoulli equation: 4V2 + right atrial pressure, where V is the tricuspid regurgitant jet velocity (TRV). PASP values of 36 – 49mmHg indicate possible PH while values of 50mmHg or more indicate likely PH [2].

The prevalence of PH in ESRD ranges from 18.8-68.8% [2,3]. However epidemiologic data for this disorder is based mainly on retrospective data from small studies with methodological limitations. Only the PEPPER study by Pabst et al [13] has measured PASP through RHC in patients with ESRD. They found a prevalence of PH of 68.8%, though the study was biased as it included only ESRD patients already having symptomatic dyspnea.

Dialysis-associated PH falls into group five of the WHO classification [1] of PH. It is increasingly being recognized that PH in ESRD may be to diminishing kidney function, rather than an underlying disease process. Contributing factors include volume overload, haemodialysis using arteriovenous fistulae (AVF), exposure to dialysis membranes, severe anaemia, left ventricular (LV)and endothelial dysfunction and pulmonary vascular calcification and rigidity [2,3,4,5]. Longer duration of haemodialysis has been found to be significantly associated with PH in ESRD [4]. No specific intervention trial aimed at reducing PH in patients with ESRD has been performed. Further insight into predisposing factors and aetiopathogenesis may allow us to institute prevention strategies and treatment.

PATIENTS AND METHODS

Objectives

Primary Objective: To determine the prevalence of pulmonary hypertension among patients with ESRD undergoing haemodialysis at KNH, using Doppler echocardiography

Secondary Objective: To explore possible associations between PH in these patients and the duration of haemodialysis, number of dialysis sessions per week, volume overload, presence of AVF, severe anaemia and left ventricular dysfunction.

Procedures: This cross-sectional study included 117 patients from the Kenyatta National Hospital (KNH) renal unit who were 13 years or older and gave written informed consent or assent for those less than 18 years of age. Patients were excluded if they had a previous diagnosis of congenial or valvular heart disease, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary thromboembolism, deep venous thrombosis, connective tissue disease or HIV and if written informed consent or assent was not obtained.

A brief history was taken from each patient to confirm duration of haemodialysis, number of haemodialysis sessions per week, dry weight and vascular access history. Both before and after haemodialysis, the patient's weight was measured in Kilograms to the nearest 100grams and a physical examination done to compare for features of fluid overload. Signs and symptoms of fluid overload noted included lower limb oedema, raised jugular venous pressure (JVP) and / or pulmonary oedema. Because the patients' dry weight change as they gain or lose lean mass, volume overload was defined as failure to achieve dry weight PLUS a clinical feature of volume overload.. Blood was drawn from all patients to screen for anaemia as part of the secondary objectives of the study. The patient's HIV status was determined as per the file diagnosis.

Echocardiography

All transthoracic echocardiographs were performed using a single machine, the Sonosite Fujifilm M-turbo with a 2.5Hz multi-frequency transducer. All echocardiographs were performed by a single experienced dedicated sonographer in order to reduce inter-observer variability in image acquisition. Echocardiography was done under the supervision of an experienced cardiologist who reviewed all images and measurements after they were acquired. Prior to the execution of the study, consensus was achieved between the cardiologist, principal investigator and sonographer on the methodology of acquisition and measurement of images, to ensure uniformity of definitions and standardization of measurement. All echocardiographic data was stored on a hard-disk.

All echocardiographs were performed within two hours of haemodialysis in an attempt to minimize the effect of volume overload on pulmonary pressures. All measurements during echocardiography were taken over at least 6 cardiac cycles. Each patient underwent echocardiography for the measurement of three main parameters:

a) Pulmonary arterial systolic pressure (PASP):

To determine PASP using the modified Bernoulli equation, the TRV was measured using continuous wave Doppler echocardiography in the apical four chamber view then added to the RAP. RAP was estimated using IVC diameter and its degree of inspiratory collapse [18].

Mean RAP is been recommended rather than a range [18]; hence IVC diameter up to 2.1 cm that collapsed more than 50% with a sniff suggested normal RA pressure of three mmHg, whereas IVC diameter more

than 2.1 cm that collapsed less than 50% with a sniff suggested high RA pressure of 15 mmHg. In situations that did not fit the above two scenarios, an intermediate value of eight mmHg was used [18]. IVC diameter was measured using 2D echocardiography in the short axis subcostal view, just proximal to the entrance of the hepatic veins. IVC measurements were taken just before the P-wave on the electrocardiogram during end-expiration, while avoiding Valsalva's manoeuvres.

b) LV systolic function:

Ejection fraction (EF) was used as a measure of LV systolic function. Measurements of the interventricular septum thickness, LV internal dimensions and LV posterior wall thickness at end- diastole and at end-systole were taken in the parasternal long axis view. An M-mode cursor was placed through the septal and posterior LV walls just beyond the tip of the mitral leaflets for this purpose and images taken. In the event of a regional wall motion abnormality, a second window was used to get additional values. EF was then calculated using the modified Simpson method [18].

EF = End-diastolic volume – End systolic volume x 100
End-diastolic volume c) LV diastolic function:

Pulse wave Doppler echocardiography across the mitral valve in the four chamber view was used to measure E/A ratio (Early filling velocity/Late filling), deceleration time (DT) and the isovolumetric relaxation time (IVRT) as determinants of diastolic function [18]. Based on any abnormal parameter, diastolic dysfunction could then be graded from grade one to four, where grade one is an abnormal relaxation pattern and grade four is lack of E/A reversal even with valsalva.

Data Management and Analysis

Clinical and echocardiographic variables were compared between patients with and without PH. Values were expressed as mean ± Standard deviation (SD), median and percentage for categorical parameters. Differences between groups were compared with Student's t-test for parametric continuous variables. Chi-square test was applied for estimating the occurrence of categorical variables.

RESULTS

The clinical and echocardiographic features of our study subjects are summarized in Table 2. Our sample population was relatively young, with a median age of 44 years, mean age of 44.3 years and range from 13 to 80 years and predominantly male. The prevalence of PH amongst chronic haemodialysis patients at KNH was 32.5%. Of these, 17.7% had possible PH and 14.5% had likely PH (PASP $\geq$50mmHg). The median PASP value amongst those with PH was 47.3mmHg, mean of 52.1mmHg and a range of 36.1 – 79 mmHg. The demographic and clinical profiles of the patients with pulmonary hypertension are displayed in Table 3.

As part of our secondary objectives, we explored possible associations between PH and a number of clinical and echocardiographic findings. The only statistically significant finding (P0.002) was between PH and LV systolic dysfunction, with an EF of less than 50%. This association remained significant on combining systolic and diastolic left ventricular dysfunction (P 0.029). These results are summarized in table 4.

Table 1
Summary of prevalence studies – PH in ESRD (PASP Pulmonary arterial systolic pressure, PH Pulmonary Hypertension, TRJ Tricuspid regurgitant jet velocity

Study	Study type	Study Site	N	PASP cut-off (mmHg)	Prevalence (%)
Magdy (2013)	retrospective	Saudi Arabia	65	PASP ≥35	41.53%
Pabst (2012)	prospective	Germany	31	PASP ≥25	68%
Ramasubbu (2012)	prospective	USA	90	TRJ ≥2.5m/s	48%
Etemadi (2011)	retrospective	Iran	278	PASP ≥35	41.1%
Yigla (2009)	prospective	Israel	127	PASP ≥45	29.1%
Bozbas (2009)	retrospective	Turkey	432	PASP ≥30	18.8%
Mahdavi (2008)	prospective	Iran	62	PASP ≥35	51.6%
Nakhoul (2005)	prospective	Israel	42	PASP ≥25 at rest or ≥35 with exercise	48%
Yigla (2003)	prospective	Israel	58	PASP ≥35	39.7%

Table 2
Sociodemographic and clinical features of hemodialysis patients at Kenyatta National Hospital (AVF Arteriovenous fistula, EF Ejection Fraction, PASP Pulmonary arterial systolic pressure)

	Haemodialysis patients (n=117)
Age (years)	44.35
Male gender	74 (63.2%)
Duration on haemodialysis (years)	2.13
Twice weekly haemodialysis	87 (74.4%)
Presence of AVF	46 (39.3%)
Hypertensive	102 (87.2%)
Diabetic	32 (27.4%)
PASP (mmHg)	26.12
EF (%)	59.44
Haemoglobin (g/dl)	9.15

Table 3
Demographic and clinical characteristics in PH and non-PH groups (PH Pulmonary Hypertension)

Variable	PH (n=38)	No PH(n=79)	Odds Ratio (95%CI)	P value
Age (years)	46.6	44.88		
Male gender	23(60.5%)	51(64.6%)	1.19(0.49-2.83)	0.672
Duration of HD (years)	2.66	1.51	NA	
Twice HD / week	28(76.4%)	59(74.7%)	1.09(0.41-3.08)	0.848
Hypertension	36(94.7%)	68(85.9%)	2.91(0.58-28.2)	0.163
Diabetes mellitus	14(36.8%)	18(23.1%)	1.98(0.77-4.97)	0.11
Clinical volume overload	7(18.4%)	12(15.4%)	1.26(0.38-3.88)	0.657
AVF	14(36.8%)	32(40.5%)	0.86(0.35-2.04)	0.704
EF (%)	54.59	62.46		
Diastolic dysfunction	21(55.3%)	45(57.0%)	0.93(0.4-2.2)	0.862
Haemoglobin (g/dl)	8.91	9.25		

Table 4
Correlations between PH and clinical and echocardiographic variables (AVF arteriovenous fistula, EF Ejection fraction, Hb Hemoglobin, PH Pulmonary hypertension)

	PH(n=38)	**Odds Ratio (95%CI)**	**P value**
Male gender	23(31.1%)	1.19(0.54-2.64)	0.672
Haemodialysis duration			
< 1 year	13(26.0%)	1	
1-5 years	22(36.7%)	1.65(0.72-3.75)	0.233
≥6 years	3(42.9%)	2.13(0.42-10.84)	0.36
Twice HD / week	28(32.2%)	0.95(0.39-2.29)	0.908
Diabetes	14(43.8%)	0.51(0.22-1.18)	0.113
AVF	14(30.4%)	1.17(0.53-2.59)	0.704
Volume overload	8(42.1%)	0.61(0.22-1.66)	0.331
EF <50%	11(68.8%)	0.17(0.05-0.52)	0.002
Diastolic dysfunction	21(31.8%)	1.07(0.49-2.34)	0.862
Anaemia			
Hb >7.5 – 10 g/dl	28(31.5%)	1	
Hb ≤7.5 g/dl (Severe anaemia)	9(33.3%)	1.09(0.44-2.72)	0.855
AVF and anaemia	4(28.6%)	1.23(0.36-4.22)	0.74
EF and diastolic dysfunction	7(63.6%)	0.24(0.06-0.86)	0.029

DISCUSSION

The prevalence of pulmonary hypertension amongst chronic ESRD patients on haemodialysis at the renal unit KNH is 32.5%. This translates to approximately one in every three haemodialysis patients with PH, which greatly exceeds the prevalence of PH in the general population, which is of 5-15 per million adult population [19]. Considering those factors that have been found to be significantly associated with PH in ESRD in previous studies [14, 15], the high prevalence of PH in our study population is likely multifactorial. Our patients dialyze twice a week at best and hence may be chronically volume overloaded. Just under a quarter (23.7%) have severe anaemia (7.5g/dl or less) whilst 94.7% are hypertensive. It is not surprising that more than half (55.3%) have LV dysfunction.

The PH group when compared to those without PH, had dialyzed for a longer duration – a median duration of 2.66 years as compared to 1.51 years; they had 3% more patients with fluid overload and 10% more patients with LV dysfunction. There were also more diabetic and hypertensive patients as compared to the non-PH group. Though none of these associations were statistically significant, the trends are similar to those found in other studies. The prevalence of PH in ESRD has been reported to range between 18.8% [13] to 68.8% [12, 13]; our study found a prevalence of 32.5%. Prevalence estimates between studies vary due to several factors. Firstly, inter-dialytic increase in volume may contribute to increased pulmonary pressures. Strength of our study was that all echocardiograms were performed within two hours of haemodialysis, hence reducing the effect of volume overload on pulmonary pressures to a minimum.

Secondly, there are various definitions of PH that have been used within the studies, ranging from PASP of 35mmHg to 45 mmHg. For example when Ramasubbu et al [20] defined pulmonary hypertension at PASP of 35mmHg or more, prevalence was 47% but on review of those with PASP greater than 45mmHg within the same study, prevalence was only 20%. Another confounder lies in the fact that there are no universally agreed upon markers of chronic volume overload, which could contribute to pulmonary pressures in variable degrees.

When compared to similar studies that used a cut-off PASP of 35mmHg (Table 5), our study had a relatively low prevalence of PH. This was surprising considering the lower number of dialysis sessions and high prevalence of anaemia [15]. However, majority of our patients were male and younger compared to many of the previous studies [4]. An increased prevalence of PH may be expected where more patients are female, due to APAH in connective tissue disease. The prevalence of PH has also been found to increase with age [4]. In the studies by Agarwal et al, Magdy et al and Mahdavi et al, 68%, 100% and 100% of patients respectively dialyzed using AVF; only 39.3% of our patients had AVF and this may further explain why we have lower prevalence of PH. Mahdavi et al performed echocardiograms within 24 hours of last haemodialysis as compared to our two-hour interval; the high prevalence of PH in their study could be accounted for by intravascular volume increase during that time period.

Table 5
Comparison of selected findings by Soki et al with similar studies (HD hemodialysis,

Variable	Soki et al (2015)	Magdy et al (2013)	Agarwal et al (2012)	Mahdavi et al (2012)
Sample size	117	65	288	62
Prevalence of PH	32.48%	41.53%	38%	49.3%
Mean age PAH	46.6 years	49.92 years	56.6 years	51.1 years
Average duration of HD	2.66 years	6.69 years	-	-
% AVF	39.3%	100%	68%	100%
% male PH	63%	52.3%	65%	56.3%

AVF arteriovenous fistula, PH Pulmonary Hypertension)

Our patients had dialyzed for a mean 2.12 years compared to the 6.69 years in the study by Magdy et al; the prevalence of PH has been found to be significantly associated with the duration on HD4. Short duration of HD in our patients may be due to increased mortality in this population or early kidney transplantation. As a secondary objective, our study sought to explore associations between PH and clinical, echocardiographic and laboratory parameters. We found LV dysfunction to be a statistically significant independent determinant of PH (P=0.002). PH is a frequent and major consequence of left heart failure. The prevalence of PH in systolic HF ranges 68-78% in advanced disease due to pulmonary venous hypertension [21]. The PEPPER study by Pabst et al [13] used right heart catheterization to evaluate PH in ESRD patients; 65% had post-capillary PH secondary to LV dysfunction. Kidney disease causes LV dysfunction through chronic volume overload, uncontrolled hypertension, myocardial ischemia caused by vascular calcification, endothelial dysfunction, dyslipidaemia and dysautonomia.

No association was found between PH and presence of an AVF, fewer sessions of dialysis, anaemia or diastolic dysfunction. This may be because of the small number within our study population who had AVFs and the lower proportion of females. Further, a recent study published by Unal et al [22] has concluded that the creation of an AVF has no significant effect on the development of PH in the short term; as previously noted, our patients had only been on haemodialysis for a mean duration of 2.66 years.

There were some limitations to this single center study. Due to financial constraints, we were unable to confirm the aetiology of the PH in our study population using imaging, spirometry and RHC. The measurement of volume overload was subjective and unable to detect silent over-hydration. Information from the patient on their medical history could have been subject to recall bias.

CONCLUSION

The prevalence of PH is high amongst haemodialysis patients at KNH and warrants screening via Doppler echocardiography. There was a strong association between PH in ESRD and LV systolic dysfunction. Further studies shall be required to establish the accuracy of the correlation between PH and left ventricular

systolic dysfunction in this population as this may be an important point of intervention for reduction of morbidity and mortality in this population.

CONFLICT OF INTEREST

The study was partially funded by Kenyatta National Hospital. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no conflict of interest to declare.

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