Association of Pulmonary Hypertension With Inflammation and Fluid Overload in Hemodialysis Patients

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Introduction. Pulmonary hypertension (PH) has been reported in hemodialysis patients, but data regarding its pathogenesis are scarce. This study aimed to evaluate the role of fluid overload in PH and its interrelationships with the usual biomarkers of micro-inflammatory state in hemodialysis patients.

Materials and Methods. In is a cross-sectional and prospective study, 119 consecutive hemodialysis patients at a Brazilian referral university hospital were evaluated between March 2007 and February 2013. Based on the presence of echocardiographic parameters of PH, patients were allocated to two groups of the PH group and the non-PH group. Clinical parameters, site and type of vascular access, bio-impedance, and laboratory findings were compared between the two groups and a logistic regression model was elaborated.

Results. Pulmonary hypertension was found in 23 (19.0%) of 119 patients. The groups significantly differed in extracellular water, ventricular thickness, left atrium diameter, and ventricular filling. Additionally, laboratory data associated with PH were alpha-1-acid glycoprotein (140.0 ± 32.9 versus 116.0 ± 35.5; $P < .001$); C-reactive protein (median, 1.1 versus 1.6; $P = .01$) and B-type natriuretic peptide (median, 328 versus 77; $P = .03$). The adjusted logistic regression model, including alpha-1-acid glycoprotein and B-type natriuretic peptide, showed significant associations for both (odds ratio, 1.023; 95% confidence interval, 1.008 to 1.043; $P = .004$ and odds ratio, 3.074; 95% confidence interval, 1.49-6.35; $P = .002$, respectively).

Conclusions. Pulmonary hypertension, cardiac hypertrophy, fluid overload, and inflammation were associated to each other in hemodialysis patients, providing insight into its pathogenesis. Longitudinal studies are warranted.

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INTRODUCTION

Although pulmonary hypertension (PH) is an emerging risk factor for death in dialysis-dependent chronic kidney disease (CKD) patients,[1] and has been documented in approximately 20% of this population,[2] its pathogenesis remains unclear. Some studies have associated several risk factors with PH in hemodialysis patients, but further studies are

still needed. Arteriovenous fistulas, left ventricular hypertrophy, anemia, hyperparathyroidism, hyperphosphatemia, hypoalbuminemia, micro-inflammatory states, and fluid overload have been associated with PH in multiple studies.[3-6]

Micro-inflammatory state and fluid overload are interrelated and can intensify each other. In a previous study, we demonstrated the influence of sodium on the micro-inflammatory state in CKD patients.[7] We also showed that fluid overload and lower albumin serum levels were associated with PH in such patients.[8] However, those findings were based on a retrospective study and inflammatory biomarkers were not investigated. Thus, this cross-sectional prospective study was designed with the purpose of evaluating the role of fluid overload in PH and its interrelationships with the usual biomarkers of the micro-inflammatory state in CKD patients on dialysis.

MATERIALS AND METHODS

This is an observational cross-sectional and prospective study of consecutive hemodialysis patients of the Division of Nephrology of the Botucatu Medical School, São Paulo State University, Brazil, evaluated between March 2007 and February 2013. The inclusion criteria were an age greater than 18 years, being on hemodialysis for over 2 months, and availability of a good technical quality echocardiography examination. The exclusion criteria were the presence of ventricular dyskinesia or hemodynamically significant valvar disease, alcohol dependence, psychiatric disorders, hepatic cirrhosis, malignant neoplasm, acute infectious diseases, antibiotic use in the past 2 months, chronic inflammatory diseases, chronic pulmonary diseases, having a central venous catheter, and having a positive human immunodeficiency virus serology. Patients provided informed consent and the study protocol was approved by the Research Ethical Committee on Human Research of the Botucatu Medical School. All of the participants signed an informed consent form (No 41422012).

The participants were allocated into 2 groups of the PH group and the non-PH group, based on the presence of echocardiographic parameters of PH. Clinical and laboratory findings were compared between these two groups. Demographic and clinical data (comorbidities, type and location of vascular access, blood pressure, and bio-impedance) were recorded. Blood samples were collected for testing hemoglobin, C-reactive protein, alfa-1-acid-glycoprotein (AAG), B-type natriuretic peptide (BNP), creatinine, albumin, calcium, phosphorus, and parathyroid hormone levels. All of the examinations were performed before the beginning of the midweek hemodialysis within at least 2 weeks before or after the echocardiography examination.

The participants were submitted to dialytic procedures with a polysulfone dialyzer for 4 hours, 3 times a week, in controlled ultrafiltration hemodialysis machines. Dialysate and blood flux were prescribed to reach a Kt/V target of 1.4. Anticoagulation was performed by heparin bolus during the hemodialysis procedure. The blood pressure monitoring was mensured before dialysis and was considered the mean of measures immediately before each ten dialysis sections.

Echocardiographic imaging was performed between the second and third dialysis days according to a previously standardized technique,[9] by highly skilled echocardiographers using a Hewlett Packard Sonos 2000 device attached to a multifrequential 2.5 MHz to 3.5 MHz transducer. The coefficient of variation of the echocardiographic measurements in our laboratory was 2.5%. The following data were registered: diameters of the left ventricular (LV) cavity at systole and diastole, thickness of the posterior wall and the septum (both at diastole and systole), and left atrium and aorta at systole. Such data were used to calculate the relative thickness of the left ventricle, the left atrium-aorta diameter ratio, the LV mass, and LV mass index. In the absence of tricuspid regurgitation, the ratio of time to peak velocity and right ventricular ejection time inferior to 0.3 was defined as PH.[10]

When tricuspid regurgitation was identified with a continuous-wave Doppler, systolic pulmonary arterial pressure was calculated using the following equation[9,10]:

Systolic pulmonary arterial pressure = 4 × (tricuspid systolic jet)^2 + 10 mm Hg (estimated right atrial pressure)

Pulmonary hypertension was defined as a systolic pulmonary arterial pressure equal or higher than 35 mm Hg.[9,11]

Monofrequential electric bio-impedance (800 µA and 50 kHz) was performed with a Biodynamics 450

device (Biodynamics, USA),[12] 50 minutes after the end of hemodialysis, with the patients in the supine position. Patient assessments were conducted using a connection between the analyzer to the back of the hand and instep of the subject. Resistance and reactance were measured; phase angle, total body water, intracellular water, and extracellular water were calculated based on resistance and reactance. Then a microprocessor was used to store values and perform subsequent calculations according to equations described elsewhere.[12-14]

Statistical Analyses

Normally distributed variables were described as mean ± standard deviation and the frequencies as a percentage. Variables not normally distributed were described as a median and interquartile interval or range. The comparisons between the PH group and the non-PH group were performed by the *t* test for unpaired samples, the chi-square test, or the Mann-Whitney test, as appropriate. Candidate variables that were associated with PH ($P < .10$) were selected for multivariable logistic regression analysis. Potential collinearity among variables selected for multiple analysis were tested and if associations were present, one of the variables was dropped from the logistic model. Finally, a logistic model was elaborated with BNP, AAG, and age. Results were considered significant at a *P* value less than .05. Statistical analysis was performed the SPSS software (Statistical Package for the Social Sciences, version 12.0, SPSS Inc, Chicago, IL, USA).

RESULTS

There were 209 eligible hemodialysis patients, but 90 patients met the exclusion criteria, and 119 patients were included. There were 64 men (54%) and 55 women (46%) with a mean age of 58.0 ± 14.2 years. Pulmonary hypertension was present in 23 of the hemodialysis patients (19%).

Table 1 shows the clinical, anthropometric, and bio-impedance characteristics of the groups. The PH group presented both more extracellular mass and water. The systemic blood pressure was scantly higher in the PH group and the site and type of vascular access did not differ between

Table 1. Clinical and Bio-impedance Characteristics in Hemodialysis Patients With and Without Pulmonary Hypertension*

Characteristic	Pulmonary Hypertension Group	Non-Pulmonary Hypertension Group	*P*
Number of patients	23	96	…
Age, y	63.0 ± 14.7	57.0 ± 13.9	.07
Male	14 (61)	50 (52)	.60
Non-White	4 (25)	23 (34)	.62
Diabetic	11 (48)	40 (42)	.76
Dialysis vintage, mo	17 (7 to 39)	23 (8 to 55)	.40
Session duration, min	4 (4 to 4)	4 (4 to 4)	.56
Body mass index, kg/m^2	26.00 ± 3.85	26.70 ± 6.67	.59
Vascular access			
Venous catheter	11 (48)	41 (43)	
Arteriovenous fistula	12 (52)	12 (52)	.83
Systolic blood pressure, mm Hg	147.0 ± 12.3	142.0 ± 19.6	.18
Diastolic blood pressure, mm Hg	86.0 ± 11.2	81.0 ± 16.6	.16
Mean blood pressure, mm Hg	107.0 ± 10.7	101.0 ± 14.6	.09
Pulse pressure, mm Hg	61.0 ± 10.2	61.0 ± 21.2	.90
Phase angle, degree	5.8 ± 1.40	6.0 ± 1.20	.52
Resistance, Ω	540.0 ± 96.2	614.0 ± 109.7	< .01
Reactance, Ω	54.0 ± 14.6	64.0 ± 16.8	.01
Total body water measured, L	34.6 ± 3.08	32.6 ± 7.05	.22
Total body water predicted, L	34.8 ± 3.06	35.0 ± 6.47	.88
Total body water change, L	-0.2 ± 3.98	-2.4 ± 2.79	< .01
Interdialytic weight gain, Kg	2.60 ± 0.64	2.60 ± 1.00	.92
Fluid volume after dialysis			
Overload	11	14	
Dehydration	12	82	.001

*Value are mean ± standard deviation for normally distributed variables and median (range or interquartile range) for skewed distributions.

Table 2. Echocardiographic and Laboratory Data in Hemodialysis Patients With and Without Pulmonary Hypertension*

Parameter	Pulmonary Hypertension Group	Non-Pulmonary Hypertension Group	*P*
Systolic pulmonary arterial pressure, mm Hg	47.0 ± 10.0	30.0 ± 1.7	< .01
Left atrium, mm	46.0 ± 5.3	42.0 ± 4.8	< .01
Left atrium-aorta ratio, %	147 ± 20	133 ± 18	< .01
Left ventricular diameter in diastole, mm	50.0 ± 5.4	47.0 ± 5.6	.11
Left ventricular diameter in systole, mm	32.0 ± 8.0	29.0 ± 5.2	.10
Posterior wall thickness, mm	13.0 ± 1.8	12.0 ± 2.0	.02
Interventricular septum thickness, mm	14.0 ± 2.2	12.0 ± 2.4	.02
Left ventricular relative wall thickness, cm	0.53 ± 0.09	0.51 ± 0.105	.37
Left ventricular mass, g	329.0 ± 89.0	270.0 ± 91.1	< .01
Left ventricular mass index, $g/m^{2.7}$	90.0 ± 25.6	75.0 ± 26.0	.02
Ejection Fraction, %	72.0 ± 13.0	77.0 ± 5.7	.02
Creatinine, mg/dL	8.7 ± 3.2	9.6 ± 2.8	.17
Albumin, g/dL	3.7 ± 0.5	3.8 ± 0.3	.09
Calcium, mg/dL	8.8 ± 0.8	8.9 ± 0.8	.60
Phosphorus, mg/dL	5.3 ± 1.9	6.2 ± 8.1	.53
Calcium-phosphorus product, mg^2/dL^2	47.0 ± 18.7	49.0 ± 15.0	.54
Parathyroid hormone, pg/mL	370 (15 to 1127)	496 (42 to 2484)	.22
Hemoglobin, g/dL	11.3 ± 1.6	11.5 ± 1.6	.61
C-reactive protein, mg/dL	2.57 (3.91)	1.48 (1.28)	.02
Alpha-1- acid glycoprotein, mg/dL	140.0 ± 32.9	116.0 ± 30.5	< .01
Brain natriuretic peptide, pg/mL	898 (1232)	267 (424)	< .01

*Value are mean ± standard deviation for normally distributed variables and median (range or interquartile range) for skewed distributions.

groups. Echocardiographic and laboratory data are expressed in Table 2. The left atrium diameter, left atrium diameter indexed to aorta diameter, left ventricular mass, and left ventricular mass index were significantly larger in the PH group. Of the laboratory data associated with PH were AAG and BNP.

A model of logistic regression was adjusted to verify the effect of different confounding factors. A variable to represent volume (BNP) and another to represent inflammation (AAG) were elected and the model was adjusted for age, as well. Both AAG and BNP showed an independent significant association (Table 3). If C-reactive protein and fluid excess (measured by bio-impedance) were taken to represent inflammation and volume, respectively, the results would not change.

Table 3. Logistic Regression Results for associating clinical predictors to Pulmonary Hypertension

Factor	Odds Ratio	95% Confidence Interval	*P*
Alpha-1-acid glycoprotein	1.023	1.005 to 1.041	.01
Brain natriuretic peptide	1.001	1.001 to 1.002	.001
Age	1.043	0.998 to 1.089	.06

DISCUSSION

This study showed the association between PH, volume overload, and inflammation in a series of hemodialysis patients. We used as markers of volume the difference between total body water, measured by bio-impedance, and total body water, predicted by anthropometric formulas,[15] and the BNP level. Both change in total body water and BNP were associated with PH. Furthermore, resistance and reactance were lower in the PH group, which connotes volume overload.

Additionally, parameters of left ventricular overload: left atrium dimension, relationship between left atrium and aorta, ventricular wall thickness, left ventricular mass, and left ventricular mass index, were significantly higher among PH patients. Also, the ejection fraction of the PH patients was worse than that of the non-PH patients. Since these parameters are markers of fluid excess, the observations above corroborate the idea that PH in CKD patients is influenced by volume overload.

High levels of BNP are strongly associated with left ventricular hypertrophy and dilation, and systolic dysfunction, in CKD patients.[16] These elevations have been partly explained by chronic volume overload, as observed in our PH group.

In the same group, thickening of the septum and of the posterior wall of the left ventricle could be explained by higher blood pressure—scantily significant in these patients—induced by volume overload and the lower ejection fraction could be interpreted by higher afterload engendering a poorer systolic performance.[17]

Marginally significant lower serum albumin levels in the PH group might be justified by dilution,[8] as this group has expanded volume. Moreover, hypoalbuminemia might also indicate subclinical inflammation.[18]

Alfa-1-acid-glycoprotein is an acute phase protein with inflammatory and immunomodulating properties observed in CKD patients.[19] In the current study, PH patients present markers of volume overload as well as of inflammation. The causal relationship between volume overload and inflammation has a physiopathological explanation supported by experimental and clinical studies. Reduction of dietetic sodium in Dahl-salt sensible rats as well as reduction of sodium in dialysate in hemodialysis patients inhibit systemic inflammation.[7,20,21] Our results are in accordance with these finds because over hydration, evaluated by bio-impedance, and BNP were associated with markers of inflammation.

The current clinical classification of PH allocates the CKD-related PH in group 5, PH with unclear multifactorial mechanisms.[22] Supported by our present results, we hypothesize that volume overload induces a postcapillary PH in hemodialysis patients. Additionally, chronic volume excess associated with CKD patients' micro-inflammatory state might trigger some inflammatory mechanism in the pulmonary vascular bed causing vasoconstriction, remodeling, and microthrombotic events with consequent precapillary PH. This hypothesis can explain the results of the PEPPER study, which verified PH by right-heart catheterization in patients with chronic kidney disease on dialysis and without dialysis and observed 13% of precapillary hypertension in hemodialysis patients.[2]

Many risk factors for PH were evaluated in the present study. The association between PH, volume overload and inflammation was adjusted to age, a known risk factor to PH.[23] Body mass index, another notorious risk factor to PH,[23] was not included in the logistic regressions because this variable was homogeneous between groups. Markers of chronic kidney disease-mineral and bone disorder associated with PH were not observed in the current study, differently from other reports.[24,25] Also, the type and location of arteriovenous fistula were not associated with PH in the current study. Some authors have associated PH in hemodialysis with vascular access,[26] but not others.[3,6,27]

A few limitations must be recognized in the current study. First, it is a cross-sectional study and has the limitations inherent to such design. Second, PH was identified only by echocardiography and not confirmed by right cardiac catheterization which is the "gold standard" for confirming the diagnosis of PH and differentiating between precapillary and postcapillary HP. Nevertheless, for ethical reasons, invasive exams for research objectives are not justified. In fact, except the PEPPER study,[2] none of the previous studies on PH in hemodialysis patients evaluated pulmonary arterial pressure invasively. Thirdly, the vascular access flux was not measured; however, the local and type of access were similar and did not statistically differ between the groups. Finally, single-frequency bio-impedance was used, but this method has been validated as a useful and reliable toll to measure water volume in hemodialysis patients. Furthermore, both single-frequency bio-impedance and multiple-frequency spectroscopy are equally accurate in measuring total body water and intracellular fluid.[28]

CONCLUSIONS

Pulmonary hypertension, cardiac hypertrophy, fluid overload, and inflammation were associated with each other in hemodialysis patients, providing insight into the pathogenesis of PH in this population. Longitudinal studies are warranted.

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CONFLICT OF INTEREST

None declared.

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