

Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography in patients with end-stage renal disease on dialysis therapy



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Background: Pulmonary hypertension (PH) is one of the most important comorbidities in patients undergoing hemodialysis (HD). The goal of the present work is to determine the possible etiologic factors for its occurrence.

Methods: The prevalence of PH was estimated by Doppler echocardiography in a cohort of 100 patients aged 49.3 ± 13.9 years on regular HD. Mean pulmonary artery pressure was estimated from pulmonary acceleration time by Mahan's regression equation. Pulmonary vascular resistance and pulmonary capillary wedge pressure were calculated. We focused on the effect of HD on left and right ventricle diastolic and systolic function. Right ventricle systolic function was assessed by tricuspid annular systolic excursion and pulsed Doppler myocardial performance index. Since impaired endothelial function was postulated as an underlying cause of PH, we studied the effects of HD on brachial artery endothelial function.

Results: The current study found that pulmonary hypertension was prevalent in 70% of patients on dialysis. Left atrium diameter, left ventricle mass indexed to body surface area, and mitral E/E' were increased in the dialysis group (4.4 ± 0.2 cm, 126.5 ± 24.6 g/m², and 16.9 ± 4.4 , respectively, $p < 0.001$ for all). Pulmonary artery systolic pressure was positively correlated to duration of dialysis and negatively correlated to glomerular filtration rate ($p < 0.001$ and $r = -0.991$). Pulmonary vascular resistance was significantly increased in dialysis patients (1.9 ± 0.2 Wood units vs. 1.2 Wood units in controls, $p < 0.001$). Endothelial dysfunction, defined as brachial artery flow mediated dilatation $< 6\%$, was found in 46% of dialysis group.

Conclusion: Increased pulmonary artery systolic pressure in the HD population could be attributed to left atrium dilatation and left ventricle diastolic dysfunction. Pulmonary vascular resistance was significantly increased in dialysis group. This might be explained by impaired endothelial nitric oxide synthesis that not only caused systemic vasoconstriction but also affected the pulmonary vasculature.

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Introduction

Pulmonary hypertension (PH) is a complex hemodynamic alteration that may result from disparate causes. In the 2008 classification by the World Health Organization and in more recent guidelines by the European Society of Cardiology, for the first time attention was given to PH in dialysis patients classified in the fifth category gathering various forms of PH with unclear etiology [1].

The high prevalence of PH was attributed to high cardiac output secondary to the presence of arteriovenous fistula, anemia, and/or and to left ventricular (LV) disorders [2]. Moreover, sleep apnea, accumulation of endogenous inhibitors of nitric oxide synthase, insult to pulmonary microcirculation attributable to exposure to dialysis membranes is likely to contribute to the unique propensity of dialysis patients to PH [3]. Our aim was to study the contribution of left and right ventricle dysfunction to pulmonary hypertension. The second aim was to show that simple echocardiographic equations can be used to assess systolic, mean pulmonary artery pressure and pulmonary vascular resistance that might help in evaluation and risk stratification of patients on dialysis

Patients and methods

Forty healthy controls and 100 adult patients aged 49.3 ± 13.9 years on regular hemodialysis (HD) for at least 12 months (range, 12–80 months) were referred from the Nephrology Department of Cairo University, Cairo, Egypt for echocardiography. Written consent was given by all the participants. The study protocol was approved by the Ethics Committee at Cairo University Hospital.

Inclusion criteria were: adults aged ≥ 18 years, stage 4 or 5 chronic kidney disease (CKD) defined as serum creatinine ≥ 2.26 mg/dL or glomerular filtration rate (GFR) ≤ 30 mL/min/1.73 m² assessed by MDRD4-formula [4] on HD, and in World Health Organization functional class \geq II with dyspnea unexplained by other causes. Exclusion criteria were: pregnancy; LV ejection fraction (EF) $< 50\%$; mitral or aortic regurgitation $>$ Grade 2; myocarditis; endocarditis; pericarditis; severe chronic obstructive pulmonary disease; lung fibrosis; and known pulmonary artery hypertension-reducing medication with prostanoids, endothelin receptor antagonists, or phosphodiesterase-5 inhibitors.

Patients were subjected to history taking, physical examination, and demographic parameters, including age, sex, and body mass index.

Abbreviations

PH	pulmonary hypertension
HD	hemodialysis
PA	pulmonary artery
PAP	pulmonary artery pressure
PVR	pulmonary vascular resistance
TRV	tricuspid regurgitant velocity
TVI	right ventricular outflow tract time-velocity integral
PCWP	pulmonary capillary wedge pressure
FMD	flow mediated dilatation
LV	left ventricle
GFR	glomerular filtration rate
MDRD	formula Modification of Diet in Renal Disease formula
WHO FC	World Health Organization functional class
LVEF	left ventricular ejection fraction
LVMI	left ventricular mass index
EACVI	European Association of Cardiovascular Imaging
ASE	American Society of Echocardiography
LA	left atrium
LAVI	left atrium volume index
RV	right ventricle
TDI	tissue Doppler imaging
TAPSE	tricuspid annular plane systolic excursion
MPAP	mean pulmonary artery pressure
AT	pulmonary acceleration time
SPAP	pulmonary artery systolic pressure
RAP	right atrium pressure
TTE	transthoracic echocardiography
LVH	left ventricle hypertrophy
MPI	myocardial performance index
AVF	arteriovenous fistula
TPG	transpulmonary pressure gradient
RHC	right heart catheterization
CKD	chronic kidney disease

Echocardiography studies were performed using a commercial scanner (iE33; Philips Medical System, Andover, MA, USA) according to the recommendations of the American Society of Echocardiography [5].

M-mode echocardiography

LV dimensions, wall thickness and functions were studied. LV mass was calculated using the Devereux formula [6]:

$$\text{LV mass(g)} = 0.8 \times 1.04 \times [\text{LVID} + \text{PWT} + \text{IVST}]^3 - [\text{LVID}]^3 + 0.6 \text{ g}, \quad (1)$$

where LVID is the left ventricle internal dimension, PWT is the posterior wall thickness, IVST is the inter-ventricular septal thickness, 1.04 is the specific gravity of the myocardium, and 0.8 is the correction factor. The LV mass index (LVMI, g/m²) was defined as LV mass divided by body surface area (m²). The reference ranges used to define LV hypertrophy (LVH) was LVMI > 115 g/m² and 95 g/m² for men and women, respectively [5]. We tried refinements in image processing according

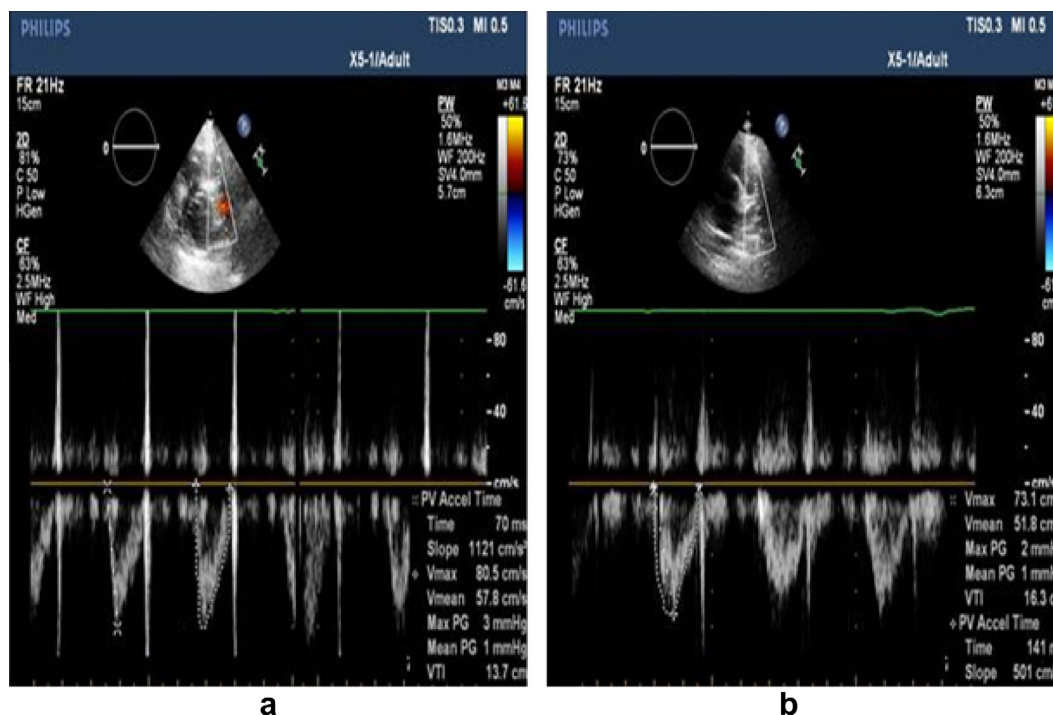


Figure 1. Pulmonary acceleration time (a) 70 ms in dialysis patient and (b) 141 ms in a control participant.

to the current American Society of Echocardiography ASE/European Association of Cardiovascular Imaging (EACVI) guidelines in order to measure the actual visualized thickness of the ventricular septum and other chamber dimensions as defined by the actual tissue–blood interface, rather than the distance between the leading edge echoes, which had previously been recommended [7].

Left atrium study

Linear dimension of the left atrium (LA) is the anteroposterior diameter in the parasternal long-axis view using M-mode echocardiography.

From the apical four chamber views maximum left atrium volumes were calculated using the area–length method according to the guidelines of the American Society of Echocardiography. Maximum volumes were divided by body surface area to calculate the LA volume index (LAVI) [5]

Right ventricle study

Our study was designed to evaluate the effect of HD on right ventricular (RV) diastolic function and systolic functions. Distal RV outflow diameter was studied using the inner-edge-to-inner-edge method according to the recent guidelines just proximal to the pulmonary valve at end-diastole [5]. Tricuspid inflow velocities were recorded using pulsed wave Doppler with the sample volume placed at the tip of the tricuspid valve tips from the apical four-chamber view. Peak E and A wave

velocities and E/A ratio were studied. The cut off for diagnosis of impaired RV diastolic function is <0.8 [5]. The average early diastolic velocity of the tricuspid annulus E' was obtained by tissue Doppler imaging (TDI) of the septal and lateral sides of the tricuspid annulus. Right-sided E/E' was used to assess filling pressure of the RV.

RV systolic function was assessed by RV myocardial performance index (Tei index) using pulsed Doppler method and tricuspid annular plane systolic excursion (TAPSE) using M-mode echocardiography.

Pulsed Doppler echocardiography

Mitral inflow velocities were recorded using pulsed wave Doppler with the sample volume placed at the tip of the mitral valve tips from the apical four-chamber view. From the mitral valve inflow velocity curve, the following measurements were made: peak E, A wave velocities, and E/A ratio. The average early diastolic velocity of mitral annulus E' was obtained by TDI of the septal and lateral sides of the mitral annulus. Pulmonary capillary wedge pressure (PCWP) was calculated according to the formula:

$$1.24 \times (E/E') + 1.9 \text{ [8].} \tag{2}$$

Color Doppler flow propagation velocity

Color Doppler M-mode imaging can be applied in the apical views to assess the velocity and rate

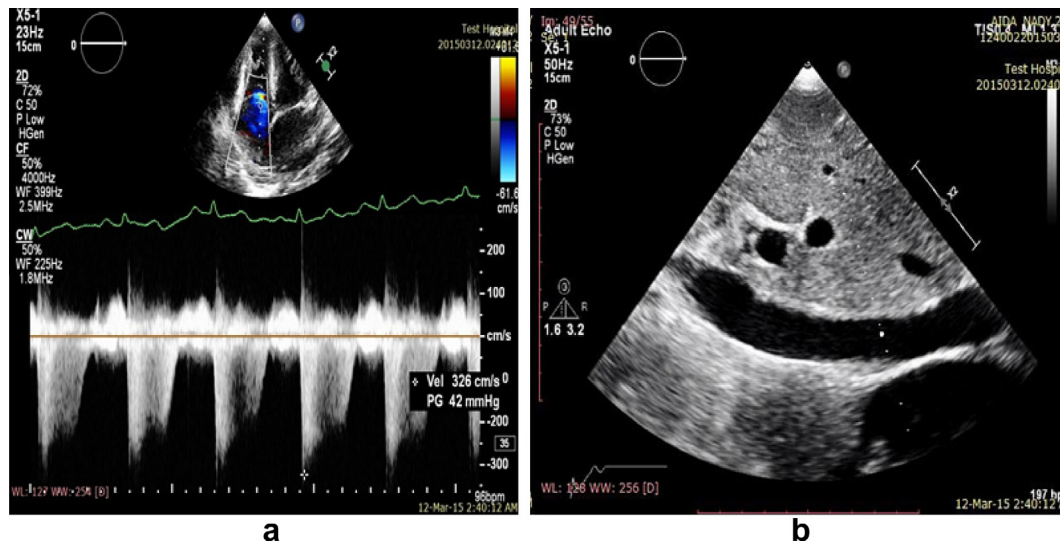


Figure 2. (a) Right ventricle systolic pressure with the Bernoulli equation formula. (b) Right atrial pressure calculated on the basis of inferior vena cava diameter.

of blood flow from the mitral valve annulus to the LV apex. In this way, the early diastolic filling wave by color m-mode, which appears in red, as blood flow from the mitral valve level to the LV apex can be identified. The slope of this early diastolic color m-mode wave (V_p), is rapid (vertical) in patients with normal diastolic function due to rapid diastolic suction in which blood quickly flow from mitral valve to LV apex. However, in the presence of increasingly impaired relaxation, this slope becomes flatter, reflecting increasingly impaired LV relaxation E/V_p ratio has therefore been developed and correlates to mean LA pressure [9,10]. Moreover, $V_p > 50$ cm/s is considered normal and E/V_p ratio ≥ 2.5 predicts PCWP > 15 mmHg with reasonable accuracy [11].

Mean pulmonary artery (PA) pressure (MPAP) was estimated using pulmonary acceleration time AT measured by pulsed Doppler of the PA in systole, whereby (Fig. 1):

$$\text{mean PA pressure} = 79 - (0.45 \times \text{AT}) \quad [12] \quad (3)$$

Continuous Doppler echocardiography

Echo-Doppler studies can provide an estimate of the pulmonary artery systolic pressure calculated on the basis of the tricuspid regurgitation jet velocity in absence of pulmonary stenosis. Pulmonary artery systolic pressure (SPAP: assumed to be equal to right ventricle systolic pressure) can be estimated with the Bernoulli equation formula:

$$4 \times \text{TRV}^2 + \text{RAP}, \quad (4)$$

where v is the maximum velocity of the tricuspid valve regurgitant jet, measured by continuous wave Doppler,

added to the estimated right atrial pressure (RAP) calculated on the basis of the inferior vena cava diameter and the extent of its inspiratory collapse [13] (Fig. 2).

Pulmonary vascular resistance (PVR) was obtained using the equation:

$$\text{PVR} = \text{TRV}/\text{TVIRVOT} \times 10 + 0.16 \quad (5)$$

where TRV is peak tricuspid regurgitant velocity and TVIRVOT is right ventricular outflow tract time-velocity integral. A normal PVR is < 1.5 Wood units (120 dynes cm/s^2), and significant pulmonary hypertension is defined as a PVR > 3 Wood units (240 dynes cm/s^2). The estimation of PVR is not adequately established to be recommended for routine use but may be considered in patients in whom SPAP may be exaggerated by high stroke volume or misleadingly low (despite increased PVR) by reduced stroke volume [14,15].

Brachial flow-mediated vasodilatation

An iE33 Philips color Doppler ultrasound scanner, Andover, MA, USA was used in this study. All imaging procedures were conducted by professionally trained operators. The brachial artery diameter was measured using the ultrasound scanner with a 7-MHz linear array probe [16]. In the dialysis group, the brachial artery diameter was measured on the nonarteriovenous fistula side, whereas the diameter of the right brachial artery was measured in the control groups. The longitudinal section of the brachial artery 5 cm above the elbow was scanned with the upper extremity abducted to 15° and the forearm supinated. Diastolic diameter of the resting brachial artery was recorded as the baseline diameter. The blood pressure was raised to 220 mmHg (to exceed the systolic blood pressure by at least 50 mmHg), and the deflation was sustained for

Table 1. Baseline characteristics.

Clinical parameters	Patients on hemodialysis (n = 100)	Control (n = 40)	p
Age (y)	49.3 ± 13.9	49.3 ± 14	NS
Sex	52F/47 M	20F/20 M	NS
Body mass index (kg/m ²)	25.0 ± 1.6	26 ± 7.2	NS
Waist circumference (cm)	114.4 ± 14.5	90.6 ± 11.7	<0.001
Systolic blood pressure (mmHg)	142.9 ± 9.5	129.4 ± 8.0	<0.001
Diastolic blood pressure (mmHg)	90.1 ± 7.8	78.4 ± 6.9	<0.001
Duration of dialysis (mo)	38.7 ± 20	—	—
<i>Underlying renal disease, n (%)</i>			
Chronic glomerulonephritis	10 (10)		
Diabetic nephropathy	33 (33.3)		
Hypertensive nephrosclerosis	16 (16.7)		
Polycystic kidney syndrome	13 (13.3)		
Others	26 (26.7)		
<i>Laboratory data</i>			
Hemoglobin (g/dL)	9.7 ± 0.9	14.5 ± 0.3	<0.001
Serum creatinine (mg/dL)	7.8 ± 1.1	0.6 ± 0.0	<0.001
Serum potassium (mEq/L)	5.4 ± 0.2	3.9 ± 0.2	<0.001
Serum calcium (mg/dL)	8.3 ± 0.8	9.3 ± 0.1	<0.001
Residual GFR (mL/min/1.73 m ²)	21.9 ± 4.9	96.8 ± 2.5	<0.001

Continuous data are expressed as mean ± standard deviation.
GFR = glomerular filtration rate; NS = not significant.

4 minutes. Flow mediated dilatation was calculated as:

$$\frac{(\text{diameter after arterial occlusion} - \text{baseline diameter})/\text{baseline diameter} \times 100.}{(6)}$$

Normal endothelial functions were defined as flow mediated dilatation (FMD) >6%; thus, FMD ≤6% was considered to indicate endothelial dysfunction [17].

Statistical analysis

Data were analyzed using IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using Student *t* test. Pearson product-moment was used to estimate correlation between numerical variables. All tests were two-tailed. A *p* value <0.05 was considered significant.

Results

From September 2014 to June 2015, 100 consecutive patients with severe CKD stage 4 or 5 on regular HD and 40 age- and sex-matched controls were screened by transthoracic echocardiography

for study participation. Baseline characteristics of the study population are shown in Table 1.

Laboratory investigations showed a significant increase in serum creatinine and potassium and decrease in blood hemoglobin, calcium and GFR in the HD group compared with the control group (*p* < 0.001 for all).

Of the 100 patients, 66 patients had E/E' ratios >15 (which identifies an abnormally elevated LV filling pressure) [18]. Using Pearson correlation an elevated E/E' ratio >15 was negatively correlated to GFR (correlation coefficient *r* value = -0.991), positively correlated to SPAP and LA diameter (*p* < 0.001, for all). Color M-mode propagation velocity was significantly decreased in dialysis group (45.3 ± 3.2 cm/s vs. 66 ± 2.3 cm/s in control, *p* < 0.001), E/Vp ratio was 1.6 and 1.1, *p* < 0.001 in dialysis and controls respectively. Moreover, E/Vp was ≥1.5 in 52% of dialysis population (Fig. 3).

Seventy percent of the dialysis group had LVH. LVMI was positively correlated to systolic blood pressure (*p* < 0.001) and negatively correlated to hemoglobin level (*r* = -0.6). Left atrium diameter and indexed maximum volumes were significantly increased in dialysis group (4.3 ± 0.5 cm and 33.5 ± 3.0 mL/m² vs. 3.4 ± 0.3 cm and 24.2 ± 2.4 mL/m² in controls (*p* < 0.001 for both; Fig. 4). Other echocardiographic parameters are presented in Table 2.

Pulmonary artery systolic and mean pressure values were significantly elevated in dialysis

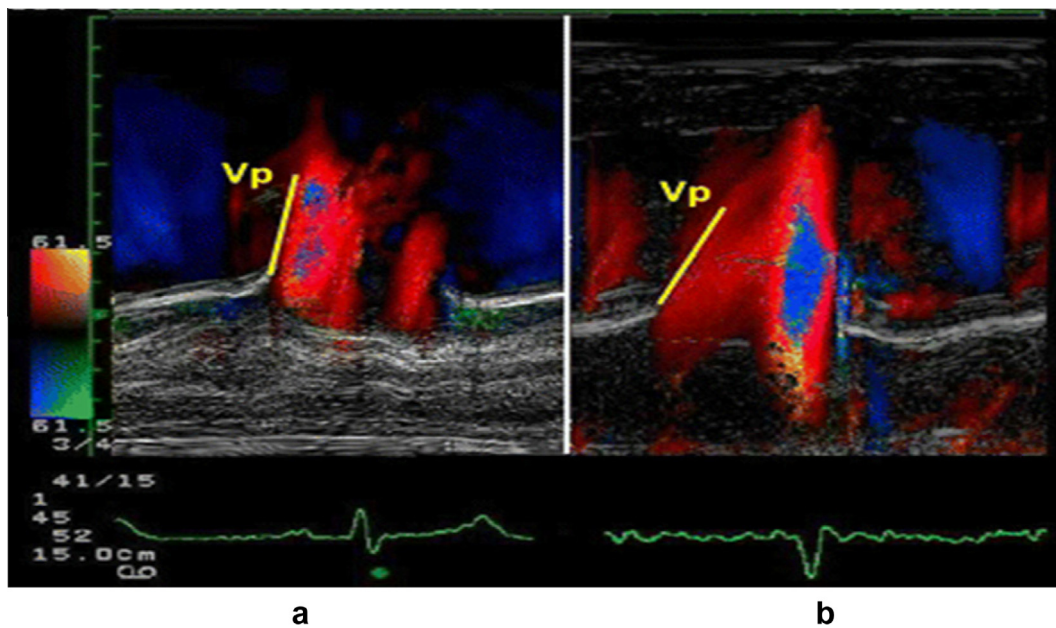


Figure 3. Transmitral flow propagation velocity (V_p): Placing the color Doppler sample volume from the mitral annular level to the left ventricular (LV) apex, the more rapid the LV relaxation, the faster blood travels from the mitral annular level to the LV apex, and hence the more vertical the color Doppler mitral inflow M-mode and the more rapid the V_p slope (a). By contrast, the more impaired the LV relaxation, the slower blood flows from the mitral annular to the LV apex, hence a flatter V_p slope (b).

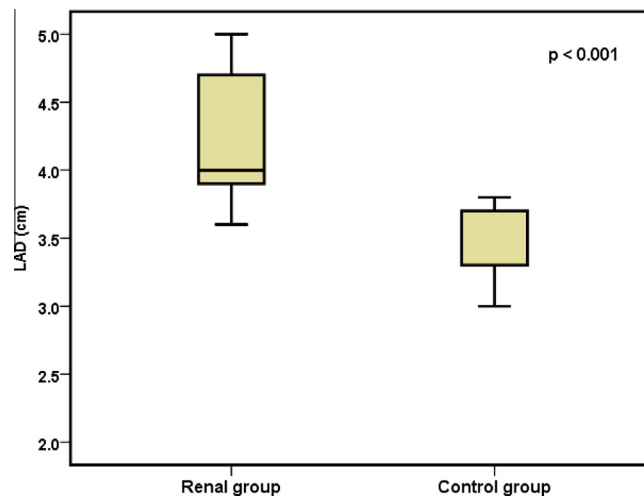


Figure 4. Left atrium diameters (LAD, cm) in dialysis and control groups.

group (46.5 ± 8.4 mmHg and 36.5 ± 8.3 mmHg, respectively). All patients with diagnostic criteria of pulmonary hypertension had PCWP ≥ 15 mmHg.

Pulmonary artery systolic pressure was positively correlated to duration of dialysis ($r = 0.9$; Fig. 5) and negatively correlated to GFR ($p < 0.001$ and $r = -0.9$; Fig. 6). Moreover, LA diameter and mitral E/E' are positively correlated to SPAP ($p < 0.001$).

Echo-derived PVR was significantly increased in dialysis patients (1.9 ± 0.2 Wood units vs. 1.2 Wood units in controls, $p < 0.001$).

Tricuspid E/A ratio and E/E' values were 0.9 and 5.7 in the dialysis group vs. 1.3 and 3.8 in controls, respectively ($p < 0.001$ for both). RV E/A ratio < 0.8 was found in 40% of the dialysis group.

RV myocardial performance index (MPI) defined as the ratio of total isovolumic time divided by ejection time was studied using the pulsed Doppler method. Ejection time is determined from the parasternal short-axis view at the pulmonary valve, based on the pulsed wave Doppler signal at the right ventricular outflow tract while isovolumic intervals are derived based on the pulsed wave Doppler envelope of the

Table 2. Echocardiographic parameters of the study groups.

Echocardiographic parameters	Dialysis group (n = 100)	Control group (n = 40)	p
<i>M-mode & 2D</i>			
LVEDD (cm)	5.1 ± 0.5	4.6 ± 0.4	<0.001
LV EF (%)	54.3 ± 1.5	63 ± 0.7	<0.001
LVMI (g/m ²)	126.5 ± 24.6	81.8 ± 11	<0.001
LADs (cm)	4.3 ± 0.5	3.4 ± 0.3	<0.001
LAVI max (mL/m ²)	33.5 ± 3.0	24.2 ± 2.4	<0.001
<i>Mitral inflow velocities</i>			
E, cm/s	69.9 ± 19.8	73.9 ± 3.6	0.056
A, cm/s	72 ± 14.6	60.2 ± 1.6	<0.001
E/A ratio	0.9 ± 0.1	1.2 ± 0.02	<0.001
<i>LV diastolic filling pressure</i>			
E/E' ratio	16.9	5.5	<0.001

Data are presented as mean ± standard deviation.

A = late diastolic transmitral flow velocity; E = early diastolic transmitral inflow velocity; E/A = ratio of early to late transmitral flow velocity; EDD = end-diastolic diameter; EF = ejection fraction; LADs = left atrial diameter at end-systole; LAVI = left atrium maximum volume indexed to body surface area; LVMI = left ventricle mass index; 2D = two dimensional.

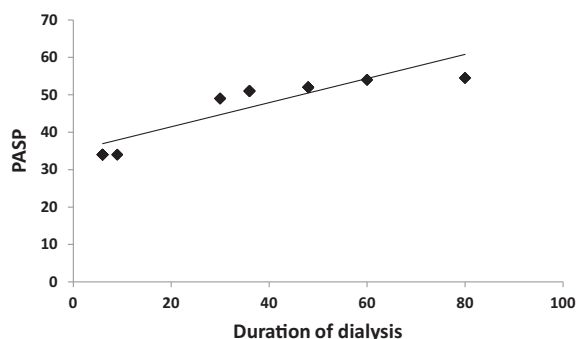


Figure 5. Duration of dialysis in months and pulmonary artery systolic pressure (PASP) in mm Hg among dialysis patients.

tricuspid flow (Fig. 7). The problem with this method is that the measurements are taken from two cardiac cycles and care must be taken to choose beats with similar R-R intervals for a more accurate assessment of the MPI. Right ventricle MPI was 0.42 in dialysis group versus 0.2 in controls ($p < 0.001$).

TAPSE was <20 mm in 65% of the dialysis group. TAPSE was 23 mm and 19 mm in controls and dialysis groups respectively ($p < 0.001$; Fig. 8).

Endothelial dysfunction

Endothelial dysfunction, defined as FMD $\leq 6\%$ was present in 46 of the 100 patients (46%). The baseline, postocclusion diameters of the brachial artery, and FMD were 3.9 ± 0.8 mm, 4.1 ± 0.8 mm, and 5.1%, respectively in dialysis patients versus 3.8 ± 0.7 mm, 4.5 ± 0.8 mm, and 18.4%, respectively, in the control group with normal endothelial function (Fig. 9).

Discussion

PA pressure may be increased by high cardiac output resulting from the arteriovenous fistula (AVF) and/or concomitant renal anemia, as well as from fluid overload [2,19,20]. Critics of this

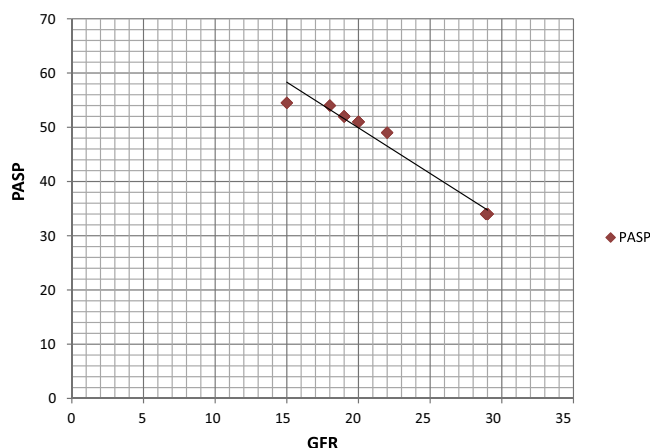
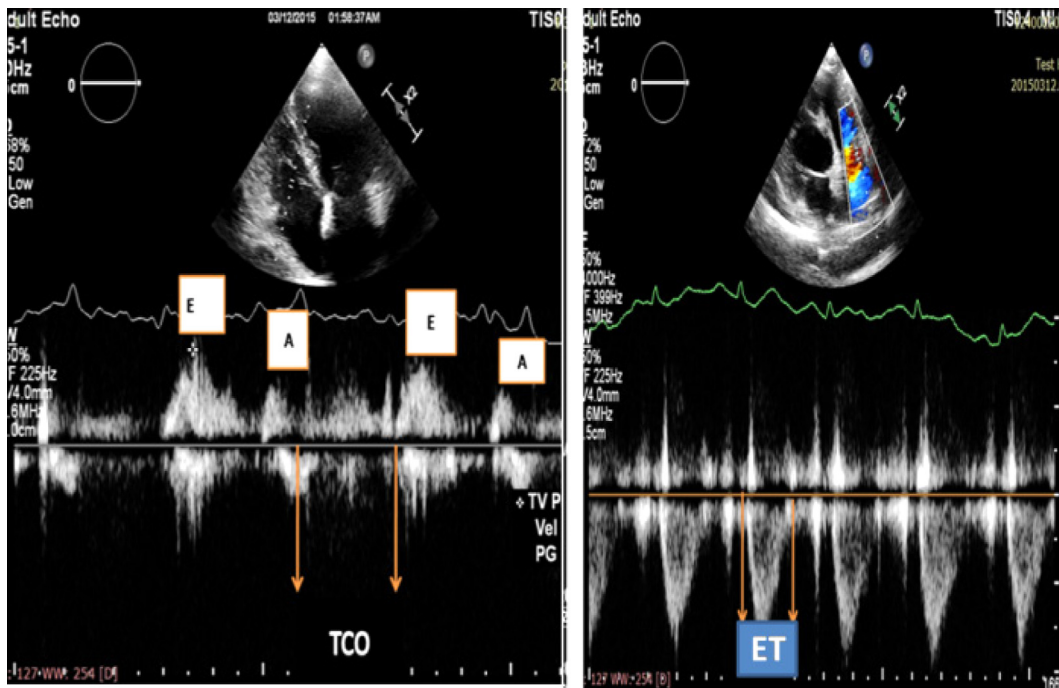


Figure 6. Glomerular filtration rate (GFR) in ml/min/1.73 m² and pulmonary artery systolic pressure (PASP) in mm Hg among dialysis group.



Evaluation of right ventricle myocardial performance index using pulmonary and tricuspid flow pulsed envelopes

Figure 7. Right ventricle myocardial performance index by pulsed Doppler envelope. $TCO-ET/ET$ where TCO is tricuspid valve closure-to-opening time and ET is ejection time.

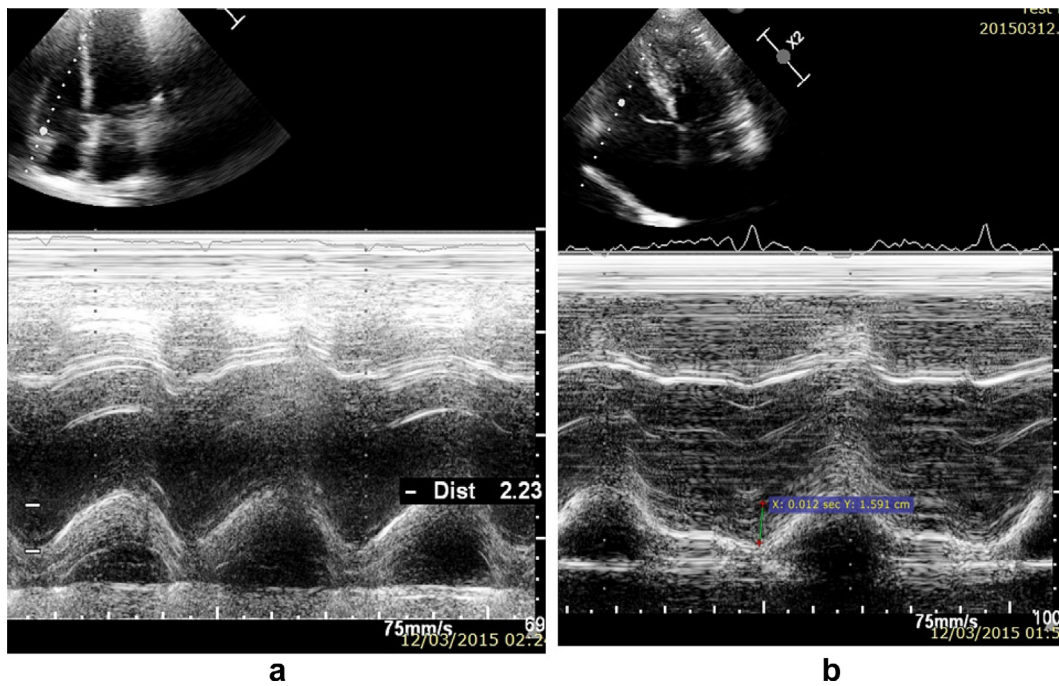


Figure 8. (a) Normal tricuspid annular plane systolic excursion; (b) tricuspid annular plane systolic excursion in a dialysis patient.

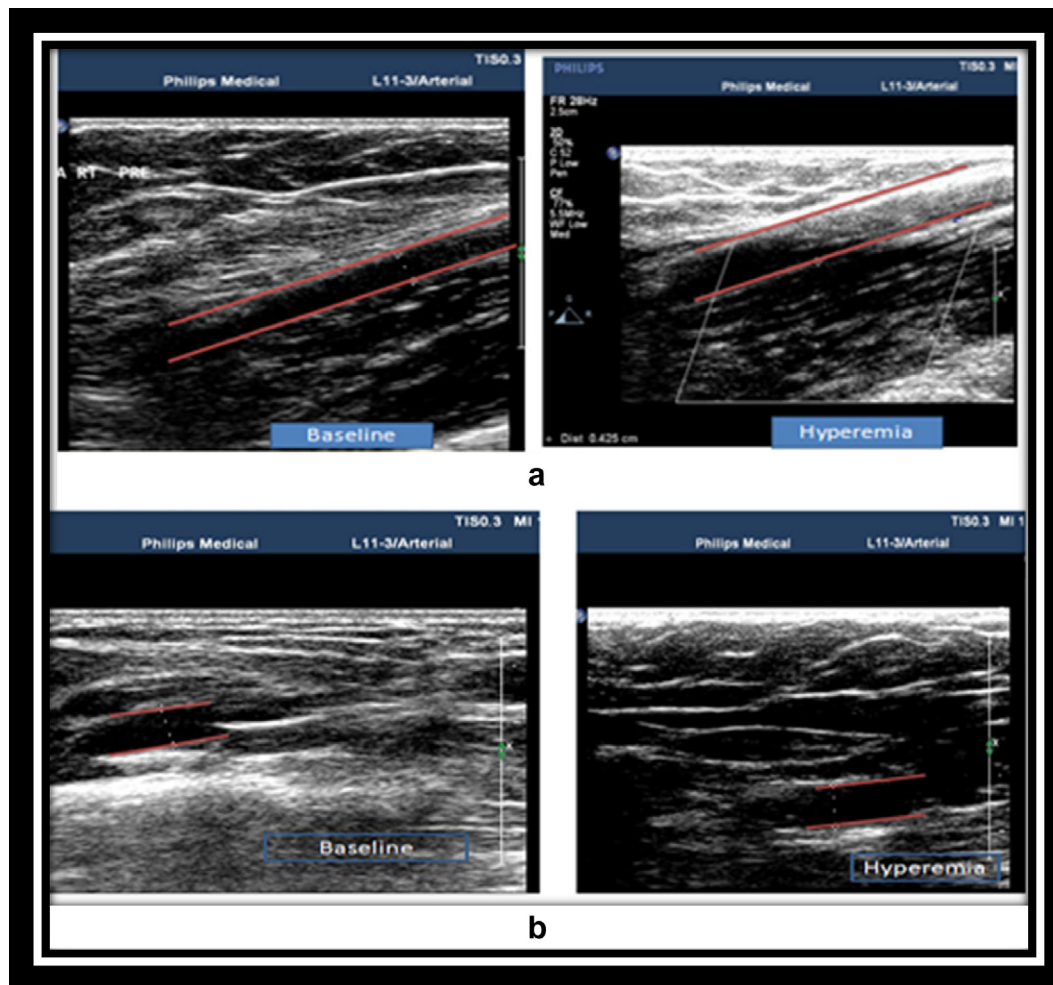


Figure 9. Flow-mediated dilatation in control (a) and dialysis patient (b).

hypothesis argue that increased venous return alone would be incapable of increasing PA pressure due to the compliant nature of the normal pulmonary vascular circulation, suggesting that either the pulmonary vasculature is noncompliant in these patients or other mechanisms are involved. Acarturk et al. [21] showed no significant difference in AVF flow between patients with PH and those without in a cross-sectional study.

Diastolic and systolic left heart dysfunctions are frequent in this setting as indicated by the high rate of post capillary PH in those patients. Some studies concluded that diastolic dysfunction was the main cause of postcapillary pulmonary hypertension in those patients [22].

Although it may be difficult to distinguish between diagnosis of precapillary PH and heart failure with preserved ejection fraction, right heart catheterization postdialysis was able to unmask precapillary PH initially masked by fluid overload in four of 25 patients of primarily postcapillary PH

[22]. There are several mechanisms that may contribute to the development of precapillary PH in patients undergoing long-term dialysis, including impaired endothelial function [23] and increased levels of endothelin-1 [24].

Mechanisms responsible for the increase in PA pressure in left heart disease are multiple and include the passive backward transmission of the pressure elevation (postcapillary passive PH). In these cases the transpulmonary pressure gradient (TPG = mean PA pressure – mean PCWP) and PVR are within the normal range. In other circumstances the elevation of PAP is greater than that of PCWP (increased TPG) and an increase in PVR is also observed (postcapillary reactive PH) [25]. Although not documented by right heart catheterization, the current study showed a high rate of postcapillary PH in dialysis patients. Since we have excluded patients with reduced LV EF, the main diagnosis in our cohort probably is LV diastolic dysfunction.

There are notable limitations of this study. PCWP may be a poor indicator of LV end-diastolic pressure; in one study about half of the patients diagnosed with PH based on PCWP <15 mmHg had elevated LV end-diastolic pressures on left heart catheterization [26]. In accordance with other studies [27], we found that PH is prevalent in 70% of dialysis patients with significant relationship between duration of dialysis and PAP. By contrast, Mousavi and colleagues' [28] study on 62 patients, found that prevalence of PH was 51.6%, and reduction in serum albumin and anemia were considered as contributing causes. Moreover, they failed to reach a significant relationship between duration of dialysis and PA pressure [28]. Concordant with others [29] LA diameter and GFR were independent determinants ($r = 0.991$, $p < 0.001$ for all) of PA pressure. The current study found that PVR was significantly increased in the dialysis group. This might be explained by impaired endothelial nitric oxide synthesis and elevated levels of endothelin that cause systemic vasoconstriction but are also likely to affect the pulmonary vasculature [30].

Methods of assessing vascular endothelial function can be classified as invasive, noninvasive, or microvascular. Sonography is the most widely used noninvasive method for clinical assessment of flow-mediated dilatation [16]. It was found that FMD of brachial artery on the nonarteriovenous fistula side of dialysis patients may closely reflect peripheral vascular endothelial function. Moreover, uremic patients have evidence of endothelial dysfunction that is accelerated by HD and the effects were associated with the duration of HD [31]. The current study showed significantly reduced FMD in dialysis patients compared to controls (5.1% vs. 18.4% in controls, $p < 0.001$). Impaired endothelial function might be the underlying cause of elevated PVR in dialysis patients. Although not verified in dialysis patients it was found that a significant inverse correlation between brachial FMD and pulmonary vascular resistance studied using right heart catheterization in patients with heart failure with preserved EF [32].

There are conflicting data concerning the LV EF in patients on HD. Paneni et al. [33] found that the EF was significantly lower in HD patients than in peritoneal dialysis patients and controls ($56.1 \pm 8.6\%$, $62.4 \pm 9.8\%$, and $68.3 \pm 5.7\%$, $p = 0.001$, respectively). However Said et al. [34] found no difference in the LV EF between the HD group and the control group ($62.50 \pm 11.6\%$ and $64.54 \pm 15.20\%$, $p = 0.525$, respectively). The

current study found that EF was significantly lower in HD (54.3 ± 1.5 vs. 63 ± 0.7 , $p < 0.001$). The LVH is highly prevalent in CKD and is associated to a clearly unfavorable prognosis. More than two-thirds of the patients undergoing dialysis with LVH die of congestive heart failure or sudden death [35]. Prevalence of LVH varies from 16% to 31% in individuals with CKD and glomerular filtration >30 mL/min 60–75% in those starting renal substitution therapy and up to 70–90% in patients undergoing regular dialysis therapy [36]. Concordantly, we found that LVH was prevalent in 80% of patients on regular HD.

As LA diameter is a strong predictor of diastolic dysfunction, the findings suggest that, in this group of patients, diastolic dysfunction may be a more relevant mechanism for PH. Recent directives recommend that the adequate quantification of the LA size be obtained by the estimate of the chamber volume in the two-dimensional mode and not by the traditional measurement of the anteroposterior diameter in the M-mode [5,37].

In the ASE/EAE guidelines, the upper normal limit for max LAVI is 34 mL/m^2 . This reference value is not only derived from population studies, but it is also based upon an estimation of risk related to chamber size, and from expert opinion [5]. We found that 40% of dialysis group had LAVI $\geq 34 \text{ mL/m}^2$. It was found that indexed LA volume $>32 \text{ mL/m}^2$ provided complementary information to the traditional clinical and echocardiographic data, including EF, E/E' ratio, and LV mass [38]. As the LV diastolic function seems to be chronically compromised in most patients undergoing HD, even in those who are asymptomatic, the LA volume can offer the opportunity to identify the individuals at higher risk to present with heart failure, atrial arrhythmias, and poor clinical evolution [38].

Palecek et al. [39] had previously found that TDI E' appears to be superior to Vp in the detection of mild to moderate LV diastolic dysfunction. However, color M-mode propagation velocity Vp was significantly decreased in the dialysis group ($45.3 \pm 3.2 \text{ cm/s}$ vs. $66 \pm 2.3 \text{ cm/s}$ in control, $p < 0.001$), E/Vp ratio was 1.6 ± 0.2 and 1.1 in dialysis and controls, respectively. Moreover, E/Vp was ≥ 1.5 in 52% of the dialysis population. The study did not compare values before and after dialysis as the load dependency of propagation velocity was previously reported by some studies that reported that TDI E' maximal velocity measured at the lateral portion of the mitral annulus appeared to be relatively preload independent and reproducible. In contrast to E', septal velocity

and Vp both appeared sensitive to abrupt preload reduction [40]. Ie and Zietse [41] reported that color M-mode Doppler is a time-consuming assessment and less sensitive in detecting milder degrees of diastolic dysfunction in dialysis patients.

It was reported that patients on HD have two peculiar clinical features: anemia and AVF; both factors lead to an increased preload on the right heart chambers [42]. Although both factors are present in our study group, no significant changes on right heart volumes were noticed because volumes return to normal ranges at the end of dialysis treatment due to reduction of extracellular fluid volumes others. Di Lullo et al. [43] found that HD led to a reduction in TAPSE in patients with AVF as opposed to central venous catheters due to the effect of preload increase operated by AVF. The current study enrolled patients with AVF and found that RV systolic function assessed by MPI and TAPSE was impaired in dialysis patients, concordant with Floccari et al. [44], who found that TAPSE was reduced <23 mm in 43% of CKD patients.

Conclusion

The mechanisms underlying development of postcapillary PH in patients on dialysis are complex. Further, prospective study utilizing right heart catheterization should be conducted to characterize patients with intrinsic increases in pulmonary vascular resistance. Increased SPAP in the HD population could be attributed to left atrium dilatation, LV diastolic dysfunction, and AVF, which causes volume overload.

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References

- [1] Galiè N, Hooper M, Humbert M, Torbicki A, Vachieri J, Barbera J, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2009;30:2493–537.
- [2] Nakhoul F, Yigla M, Gilman R, Reisner S, Abassi Z. The pathogenesis of pulmonary hypertension in haemodialysis patients via arteriovenous access. *Nephrol Dial Transplant* 2005;20:1686–92.
- [3] Agarwal R. Prevalence Determinants and prognosis of pulmonary hypertension among hemodialysis patients. *Nephrol Dial Transplant* 2012;27:3908–14.
- [4] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med* 1999;130:461–70.
- [5] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39.
- [6] Devereux R, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977;55:613–8.
- [7] Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2015;16:577–605.
- [8] Nagueh S, Middleton K, Kopelen H, Zoghbi W, Quinones M. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30:1527–33.
- [9] Rivas-Gotz C, Manolios M, Thohan V, Nagueh SF. Impact of left ventricular ejection fraction on estimation of left ventricular filling pressures using tissue Doppler and flow propagation velocity. *Am J Cardiol* 2003;91:780–4.
- [10] Dokainish H. Left ventricular diastolic function and dysfunction: central role of echocardiography. *Global Cardiol Sci Pract* 2015;3. <http://dx.doi.org/10.5339/gcsp.2015.3>.
- [11] Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;10:165–93.
- [12] Dabestani A, Mahan G, Gardin JM, Takenaka K, Burn C, Allfie A, et al. Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography. *Am J Cardiol* 1987;59:662–8.
- [13] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713.
- [14] Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. *Am Coll Cardiol* 2003;41:1021–7.
- [15] Rajagopalan N, Simon M, Suffoletto M, Shah H, Edelman K, Mathier M, et al. Noninvasive estimation of pulmonary vascular resistance in pulmonary hypertension. *Echocardiography* 2009;26:489–94.
- [16] Celermajor DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OL, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;340:1111–5.
- [17] Vogel RA. Measurement of endothelial function by brachial artery flow mediated vasodilatation. *Am J Cardiol* 2001;88:31E–4E.
- [18] Ommen S, Nishimura R, Appleton C, Miller F, Oh J, Redfield M, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures. *Circulation* 2000;102:1788–94.
- [19] Unal A, Tasdemir K, Oymak S, Duran M, Kocyigit I, Oguz F, et al. The long-term effects of arteriovenous fistula creation on the development of pulmonary hypertension in hemodialysis patients. *Hemodial Int* 2010;14:398–402.
- [20] Simonneau G, Robbins I, Beghetti M, Channick R, Delcroix M, Denton C, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:S43–54.
- [21] Acarturk G, Albayrak R, Melek M, Yuksel S, Uslan I, Atli H, et al. The relationship between arteriovenous fistula

- blood flow rate and pulmonary artery pressure in hemodialysis patients. *Int Urol Nephrol* 2008;40:509-13.
- [22] Pabst S, Hammerstingl C, Hundt F, Gerhardt T, Grohé C, Nickenig G, et al. Pulmonary hypertension in patients with chronic kidney disease on dialysis and without dialysis: results of the PEPPER-study. *PLoS One* 2012;7:e35310.
- [23] Thambyrajah J, Landray M, McGlynn F, Jones H, Wheeler D, Townend J. Abnormalities of endothelial function in patients with pre-dialysis renal failure. *Heart* 2000;83:205-9.
- [24] Tomić M, Galesić K, Markota I. Endothelin-1 and nitric oxide in patients on chronic hemodialysis. *Ren Fail* 2008;30:836-42.
- [25] Oudiz R. Pulmonary hypertension associated with left-sided heart disease. *Clin Chest Med* 2007;28:233-41.
- [26] Halpern S, Taichman D. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. *Chest* 2009;136:37-43.
- [27] Abbas F, Homayoun K, Bahador B, Fatemeh H, Bahar T. Prevalence of pulmonary hypertension in patients undergoing hemodialysis. *Iran J Kidney Dis* 2013;7:60-3.
- [28] Mousavi S, Mahdavi-Mazdeh M, Yahyazadeh H, Azadi M, Rahimzadeh N, Yoosefnejad H, et al. Pulmonary hypertension and predisposing factors in patients receiving hemodialysis. *Iran J Kidney Dis* 2008;2:29-33.
- [29] Yang Q, Bao X. Pulmonary hypertension in patients with stage 1-3 chronic kidney disease. *Genet Mol Res* 2014;13:5695-703.
- [30] Dhaun N, Goddard J, Webb D. The endothelin system and its antagonism in chronic kidney disease. *J Am Soc Nephrol* 2006;17:943-55.
- [31] Li X, Li L, Fang S, Xu Y. Effects of hemodialysis on brachial artery endothelial function. *J Ultrasound Med* 2012;31:1783-7.
- [32] Farrero M, Blanco I, Batlle M, Santiago E, Cardona M, Vidal B, et al. Pulmonary hypertension is related to peripheral endothelial dysfunction in heart failure with preserved ejection fraction. *Circ Heart Fail* 2014;7:791-8.
- [33] Paneni F, Gregori M, Ciavarella G, Sciarretta S, De Biase L, Marino L, et al. Right ventricular dysfunction in patients with end-stage renal disease. *Am J Nephrol* 2010;32:432-8.
- [34] Said K, Hassan M, Baligh E, Zayed B, Sorour K. Ventricular function in patients with end-stage renal disease starting dialysis therapy: a tissue Doppler imaging study. *Echocardiography* 2012;29:1054-9.
- [35] Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the pre dialysis population: identifying opportunities for intervention. *Am J Kidney Dis* 1996;27:347-54.
- [36] London GM, Pannier B, Guerin AP, Blacher J, Marchais SJ, Darne B, et al. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. *J Am Soc Nephrol* 2001;12:2759-67.
- [37] Tsang TS, Abhayaratna W, Barnes M, Miyasaka Y, Gersh B, Bailey K, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? *J Am Coll Cardiol* 2006;47:1018-23.
- [38] Barberato S, Pecoits R. Prognostic value of left atrial volume index in hemodialysis patients. *Arq Bras Cardiol* 2007;88:643-50.
- [39] Palecek T, Linhart A, Bultas J, Aschermann M. Comparison of early diastolic mitral annular velocity and flow propagation velocity in detection of mild to moderate left ventricular diastolic dysfunction. *Eur J Echocardiogr* 2004;5:196-204.
- [40] Vignon P, Allot V, Lesage J, Martailé JF, Aldigier JC, François B, et al. Diagnosis of left ventricular diastolic dysfunction in the setting of acute changes in loading conditions. *Crit Care* 2007;11:R43.
- [41] Ie EH, Zietse R. Evaluation of cardiac function in the dialysis patient—a primer for the non-expert. *Nephrol Dial Transplant* 2006;21:1474-81.
- [42] Yigla M, Nakhoul F, Sabag A, Tov N, Gorevich B, Abassi Z, et al. Pulmonary hypertension in patients with end-stage renal disease. *Chest* 2003;123:1577-82.
- [43] Di Lullo L, Floccari F, Polito P. Right ventricular diastolic function in dialysis patients could be affected by vascular access. *Nephron Clin Pract* 2011;118:c257-61.
- [44] Floccari F, Granata A, Rivera R, Marrocco F, Santoboni A, Malaguti M, et al. Echocardiography and right ventricular function in NKF stage III chronic kidney disease: ultrasound nephrologists' role. *J Ultrasound* 2012;15:252-6.