Original Paper

Blood Purification

Blood Purif 2017;43:18–30
DOI: 10.1159/000448986

Received: March 1, 2016
Accepted: August 9, 2016
Published online: November 23, 2016

Hemodialysis Decreases the Etiologically-Related Early Vascular Aging Observed in End-Stage Renal Disease: A 5-Year Follow-Up Study

Daniel Bia[a] Cintia Galli[b, c] Yanina Zócalo[a] Rodolfo Valtuille[d] Sandra Wray[b] Ricardo Armentano[b, c] Edmundo Cabrera-Fischer[b, c]

[a]Physiology Department, School of Medicine, Centro Universitario de Investigación, Innovación y Diagnóstico Arterial (CUiiDARTE), Republic University, Montevideo, Uruguay; [b]Instituto de Medicina Traslacional, Trasplante y Bioingeniería (IMeTTyB), Universidad Favaloro-CONICET, Solís 453, [c]Technological National University, and [d]Fresenius FME Burzaco, Buenos Aires, Argentina

Key Words
Arterial stiffness · Early vascular aging · End-stage renal disease · Hemodialysis · Pulse wave velocity · Vascular aging

Abstract
Aims: To analyze the early vascular aging (EVA) in end-stage renal disease (ESRD) patients, attempting to determine a potential association between EVA and the etiology of ESRD, and to investigate the association of hemodialysis and EVA in ESRD patients during a 5-year follow-up period. ***Methods:*** Carotid-femoral pulse wave velocity (cfPWV) was obtained in 151 chronically hemodialyzed patients (CHP) and 283 control subjects, and in 25 CHP, who were followed-up after a 5-year lapse. ***Results:*** cfPWV increased in ESRD patients compared to control subjects. The cfPWV-age relationship was found to have a steeper increase in ESRD patients. The highest cfPWV and EVA values were observed in patients with diabetic nephropathy. Regression analysis demonstrated a significant reduction of the EVA in HD patients on a 5-year follow-up. ***Conclusion:*** Patients in ESRD showed higher levels of EVA. cfPWV and EVA differed in ESRD patients depending on their renal failure etiology. CHP showed an EVA reduction after a 5-year follow-up period.

Introduction

Age-related changes with regard to the structural and functional properties of elastic arteries have been largely described and defined as vascular aging (VA) [1]. These changes include arterial stiffening and dilatation, wall thickening and endothelial function reduction [2]. VA has been shown to be accelerated in several systemic diseases accompanied or not accompanied by traditional cardiovascular risk factors in which the damage of the target organ increases the risk of cardiovascular events [2, 3]. In the last decade, the concept of early VA (EVA) has been proposed [4]; this concept makes it possible to discriminate between normal and pathological VA. The relevance of the concept of EVA lies in its association with damage in the target organ of disease [2, 5]. This new concept facilitates the understanding of the cumulative arterial damage and helps in the prevention of the risk of cardiovascular events. Therefore, identifying subjects with a burden of components of the so-called EVA syndrome in early or advanced stages could help in the designing of proper preventive interventions and/or therapeutic strategies in order to minimize target organ damage and mortality [4].

Arterial damage develops rapidly in chronic renal disease patients and leads to a high incidence in stroke, myo-

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Prof. Dr. Daniel Bia, PhD
Physiology Department School of Medicine
Director, CUiiDARTE Centre and Project, Republic University, General Flores 2125, Montevideo 11800 (Uruguay)
E-Mail dbia@fmed.edu.uy

cardial ischemia, sudden death, left ventricular hypertrophy and cardiac failure [6–9]. From initial investigations, the arterial involvement seemed to be the first and the most important determinant of the above-mentioned increases in cardiovascular disease in renal disease patients with end-stage renal disease (ESRD) [6]; these observations were confirmed by Raine et al. [10] in 1992, who demonstrated that large-arteries disease is a major contributive factor to cardiovascular morbidity and mortality in chronic kidney disease patients. Chronic kidney disease determines arterial wall changes characterized by vascular remodeling, calcifications and stiffening [7, 11]. These changes have been interpreted as an acceleration of the aging-stiffening process, also called progeria or the EVA syndrome [4, 5, 9, 11, 12].

The EVA syndrome is characterized by increases in large-artery stiffness, evaluated through the aortic pulse wave velocity (PWV) [4], which accompanies structural changes of arteries, such as elastic fiber degeneration, collagen fiber amount increase and vascular calcification [5, 11, 12]. These changes occur in association with geometrical modifications such as the increase of arterial diameter and arterial wall thickness [13, 14]. Arterial stiffness, evaluated through PWV, has shown to predict morbidity and mortality in chronic kidney disease patients beyond and above the traditional cardiovascular risk factors [9, 12, 15]. PWV measurement allows quantifying changes in arterial stiffness, determined by changes in arterial geometry and/or in the elastic properties of the arterial wall [14], being at present widely used in the carotid-femoral pathway [15]. In this context, it is noteworthy that patients with chronic renal failure show EVA. However, it remains unknown if the level of EVA depends on the etiology of ESRD. This is not a minor issue, since it would be useful to know if some causes are accompanied by a greater deleterious damage of the arterial wall.

Hemodialysis improves the survival (i.e. extends life expectancy) of ESRD patients and research aims to improve mortality by preventing anemia, diabetes, cardiac failure and atherosclerosis [16]. However, the underlying mechanisms by which hemodialysis improves survival has not yet been entirely elucidated. For example, the relationship between hemodialysis and arterial stiffness has resulted in controversial and sometimes contradictory reports [17]. Whether hemodialysis is associated with a reduction in arterial stiffness as a mechanism that contributes to reduce the accelerated progression of atherosclerotic damage in ESRD patients remains to be elucidated. On the other hand, no research has been published regarding the potential effects of chronic hemodialysis on EVA in large longitudinal clinical studies (>3-year follow-up). Hence, whether hemodialysis determines changes in EVA observed in ESRD is a hypothesis that should be verified. Moreover, in the hypothetical situation that EVA is associated to hemodialysis treatment, it is necessary to elucidate whether it is a consequence of increases in arterial blood pressure (BP) or an augmentation of vessel wall stiffness.

In this context, the aims of this study were: (1) to characterize the EVA in ESRD patients, in terms of arterial stiffness, evaluated through PWV measurements comparatively to a control group of asymptomatic age-, gender- and cardiovascular risk-matched volunteers, focusing attention on discerning a potential association between EVA and the etiology of the ESRD, and (2) to characterize the potential association between hemodialysis (5-year follow-up) and changes in EVA of ESRD.

Materials and Methods

This research was approved by our Institutional Review Board and Ethics Committee and all patients gave their written consent to be part of noninvasive studies. Procedures were in accordance with the Helsinki Declaration of 1975 (revised in 1983).

Subjects and Groups

CUiiDARTE Center and Project is a Uruguayan Interdisciplinary University Program for Arterial Disease Early Diagnosis focused on children and adults, supported by the Republic University, the Ministry of Public Health and the National Agency for Research and Innovation (ANII) [18, 19]. Using the CUiiDARTE Project database, a total of 384 asymptomatic healthy subjects were selected to comprise the control group. All of these subjects had no chronic or infectious diseases at the moment the study was carried out. They were selected in order to be matched for age-, gender- and global cardiovascular risk level (using cardiovascular risk equations) with 151 ESRD patients on hemodialysis.

In order to quantify the cardiovascular risk for each subject, we used the Framingham Risk Score (FRS) equation and the formula used by the Joint British Societies (JBS; British National Formulary, BNF), which is derived from Framingham. The FRS equation has the advantage of allowing calculations over various periods of time and for different outcomes: cardiovascular disease, stroke, coronary disease, myocardial infarction and death from either coronary or cardiovascular disease. JBS/BNF calculates cardiovascular disease risk based on the sum of the coronary disease and stroke risks given by FRS equations. To quantify FRS, we set cardiovascular disease as the outcome and 10 years as the time period. Both equations included the following variables: (1) time period (time in years over which risk is calculated), (2) patient age (years), (3) gender (male/female), (4) smoking status (smoker/non-smoker), (5) presence of diabetes (yes/no), (6) presence of left ventricular hypertrophy on ECG (yes/no), (7) brachial systolic BP (SBP; in mm Hg), (8) total cholesterol (in mmol/l) and (9) high-density lipoprotein cholesterol (in mmol/l). An MS-Excel version of these equations can be downloaded [20]. We used these equations to

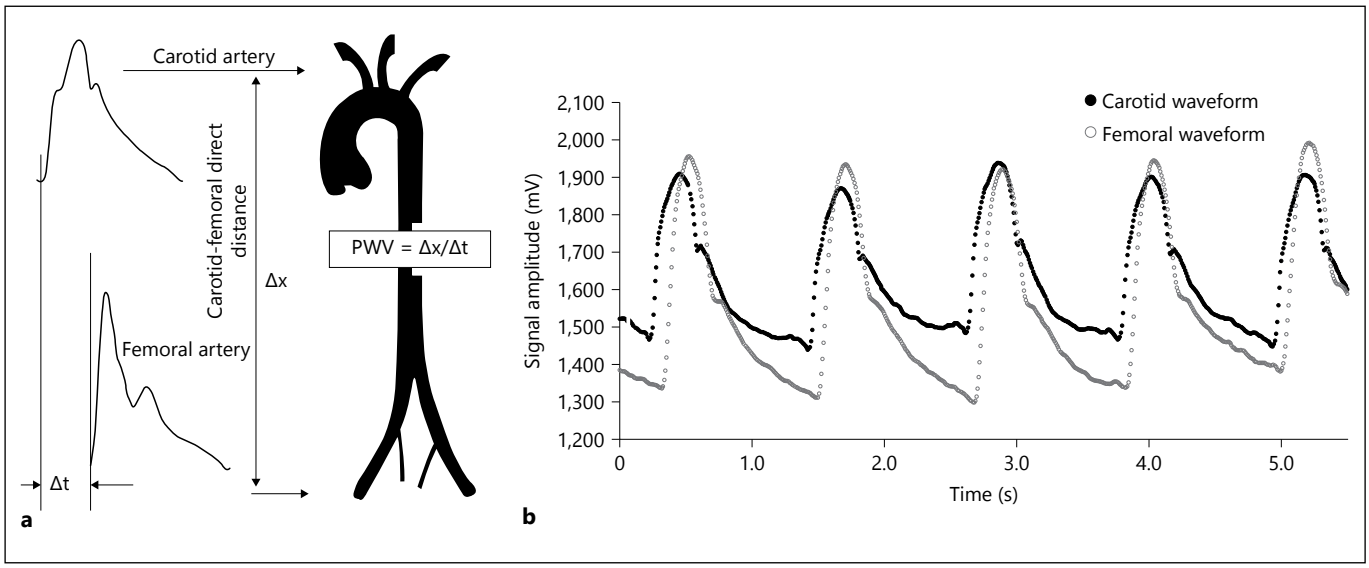

Fig. 1. a Diagram of the measurement of cfPWV: the distance between recording sites (carotid and femoral; Δx) is divided by the foot-to-foot time difference between pressure waveforms (Δt). **b** Example of carotid and femoral pulse waveforms obtained simultaneously using high-fidelity mechano-transducers. Note the 'foot-to-foot' difference.

obtain a measure of the risk to which each subject included in this study could be exposed to considering the traditional risk factors, regardless of what determined their ESRD. This matching was done to confirm that all groups have similar global cardiovascular risks following an accepted methodology.

ESRD patients were enrolled if (a) they had been on hemodialysis for at least 3 months; (b) they agreed to participate in the study, which was approved by our institutional review board, and (c) they were free of any cardiovascular complication during the 6 months preceding entry into the study. All patients were hemodialyzed 3 times a week for 4–5 h on a standard bicarbonate bath, and clinical data were monitored following routine clinical practice (pre-and post-dialysis dry body weight, body height, brachial BP, heart rate and body temperature).

The primary diseases of ESRD patients were diabetes mellitus (n = 35), unknown causes (n = 33), chronic glomerulonephritis (n = 23), tubulo-interstitial nephritis (n = 5), nephroangiosclerosis (n = 25), other causes (n = 10), polycystic renal disease (n = 16), hemolytic uremic syndrome (n = 3), amiloidosis (n = 1). No symptomatic autonomic neuropathy was confirmed in diabetic patients included in this research.

From the above-mentioned ESRD hemodialyzed patients, 25 of them had been evaluated 5 years before this research was conducted (first study: 2007; second study: 2012). In this 5-year follow-up, all data were collected by the same researchers from the same urban medical center. Data obtained from these patients were partially included in a recent investigation of the effects of hemodialysis on arterial stiffness [21].

Data Acquisition

In ESRD patients, all hemodynamic and arterial data were recorded before their scheduled midweek dialysis. Pharmacological treatment was not discontinued in any patient. In all cases, clinical data (age, heart rate, brachial BP, body weight and height) were obtained by the same observer prior to the PWV measurements. Before and during PWV recordings, brachial BP and heart rate were quantified using an automatic and validated oscillometric device, with 3 exchangeable cuffs: small (17–22 cm), medium (22–32 cm) and large (32–42 cm; Omron HEM-433INT Oscillometric System; Omron Healthcare Inc., Ill., USA). The device measures BP by using oscillometry in the range of 0–299 mm Hg, and heart rate in the range of 30–199 beats/min. The measurements were performed on the arm with no arteriovenous fistula. Measurements were done using a properly sized cuff for the circumference of the arm. Venous blood samples were drawn and processed immediately using routine laboratory methods [18, 19, 21].

The carotid-femoral PWV (cfPWV) was measured to analyze aortic regional stiffness. To this end, carotid and femoral artery waveforms were recorded using high-fidelity mechano-transducers simultaneously placed on the skin over the carotid and femoral arteries, keeping the patients in the supine position (Arteriometer, Model V100, Oxytech, Buenos Aires, Argentina) [18, 22–24] (fig. 1). Once adequate pulse waveforms were obtained during a period of 30 s, digitization was suspended. Then, carotid-femoral propagation time (Δt) was determined as the temporal foot-to-foot difference between the carotid and femoral pressure waveforms of corresponding cardiac cycles. The algorithm used to detect the so-called foot of the wave was intersecting tangents. The distance between recording sites (carotid-to-femoral distance, Δx) was then carefully measured using a measuring tape over the body surface [24]. Finally, PWV was automatically calculated as the quotient between Δx and Δt. In order to obtain 'real' cfPWV, the calculated PWV was multiplied by a scaling factor of 0.8 [22, 24]. For each record, the resulting PWV values were considered valid only if SD between measurements was <10%. The reported value for a subject was always the average of 3 recordings.

In addition, arterial stiffness was quantified using the carotid-femoral beta stiffness index (βPWV), previously reported by Shirai

et al. [25], and analyzed comparatively with other stiffness parameters by Wohlfahrt et al. [26]. βPWV represents the stiffness of the whole arterial segment that mainly comprises the aorta. This index was originally derived from the widely used 'local' arterial stiffness parameter β proposed by Hayashi et al. [27] and was expanded to some length of the artery using the modified Bramwell-Hill equation [25]:

$$\beta PWV = \ln((SBP/DBP)) \cdot (2\,\mu/PP) \cdot PWV^2, \quad (1)$$

where ln denotes natural logarithm, and SBP, diastolic BP (DBP) and pulse BP (PP) are the SBP, DBP and PP, respectively, and PWV the cfPWV. Blood viscosity was assumed as a constant value. The advantage of using this parameter (equation 1), rather than calculating PWV, is that the former is highly independent of BP; it is also suggested that it better represents structural changes of the arterial wall, maintaining a high degree of independence of the intraluminal BP levels [25, 26].

Additionally, we quantified the difference between time 1 (year 2012) and time 2 (year 2007), for each patient, in terms of: SBP, DBP, PP and mean BP (MBP), respectively, PWV and βPWV. Furthermore, the potential association between PWV o βPWV changes with variation in terms of SBP, DBP, PP o MBP was investigated.

EVA Evaluation

The following correlations between cfPWV and age were obtained: (a) in control and ESRD subjects (ESRD as an entire population), (b) discriminating sub-groups by cause (etiology) of ESRD, and (c) analyzing 2 different times of hemodialysis: time 1 (data collection conducted in 2007) vs. time 2 (data collection conducted in 2012). A similar correlation analysis was obtained using βPWV. These analyses were undertaken in order to determine the rates of age-related changes in arterial stiffness. This approach is similar to that previously reported by other authors [3, 14].

In addition, the expected theoretical value of PWV (PWV_T) was also calculated using an approach proposed by Blacher et al. [28]. These authors developed an equation (equation 2) to calculate the PWV_T for a particular subject, using several clinical parameters, including age (A; years), Gender (S; female = 2, male = 1), MBP (mm Hg) and heart period (T; ms). The following formula was based on the analysis of PWV results of these authors:

$$PWV_T = 0.0793 \cdot A + 0.0427 \cdot MBP - 0.0014 \cdot T - 0.415 \cdot S + 2.934 \quad (2)$$

This equation was derived by Blacher et al. [28] from a multivariate analysis in a population of 469 patients without ESRD. In the analysis conducted in our research, equation 2 was subsequently used in all patients with ESRD and in control subjects, in order to obtain PWV_T. Then, PWV_T was compared with the measured cfPWV (PWV_M), and the PWV index (PWV_{Index}; according with Blacher et al. [28]) was calculated as:

$$PWV_{Index} = PWV_M - PWV_T. \quad (3)$$

The analysis by Blacher et al. [28] revealed that PWV_{Index} was a strong predictor of cardiovascular and overall mortality in the population of ESRD patients undergoing hemodialysis: the higher the difference between PWV_M and PWV_T, the worse the prognosis.

Statistical Analysis

Measured and calculated parameters are expressed as mean value ± SD. Continuous variables were compared using the Student's t test or analysis of variance (ANOVA), followed by a Bonferroni test. Values expressed as percentages were analyzed through the chi-square test. Age-related changes in cfPWV (rate of change) were explored by obtaining simple linear regression models for each group and sub-group of ESRD patients and control subjects, with age as the independent variable. Differences in aging patterns were then investigated by comparing the gradients (β) of the corresponding models ($y = \alpha + \beta \cdot$ age). A correlation analysis was conducted between changes in BP levels observed in the follow-up period (from 2007 to 2012) and variations in terms of PWV and βPWV ($n = 25$). A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM-SPSS 20.0 (Chicago, Ill., USA).

Results

Data collection in control and hemodialysed patients included in this study was successfully fulfilled according to the protocol followed by the research team and above described in material and methods.

Control versus ESRD Subjects Analysis

Table 1 shows the hemodynamic, biochemical and arterial parameters obtained in a whole cohort of control (i.e. healthy) and hemodialysed patients. These data obtained from ESRD hemodialysed patients were matched with healthy subjects in terms of age, gender-distribution, and cardiovascular risk associated to classical risk factors exposition so as to include all cardiovascular risk factors in global cardiovascular risk equations. Values obtained by performing the 10-year FRS for cardiovascular disease showed that differences between control versus ESRD subjects (17.41 ± 8.46 vs. 17.56 ± 13.30%, respectively) were statistically nonsignificant. Similar results were found using the 10-year BNF equation (control: 13.95 ± 7.11% vs. ESRD: 14.45 ± 11.85%).

As seen in table 1, no differences could be demonstrated in terms of risk for cardiovascular diseases; however, aortic stiffness, in terms of PWV and βPWV, was found to be increased in ESRD patients compared to control subjects ($p < 0.001$). On the other hand, theoretical values of cfPWV calculated according the model reported by Blacher et al. [28] (PWV_T) were similar in ESRD patients when compared to control subjects. Once again, PWV_{Index} found in ESRD patients was higher than that calculated in the control group ($p < 0.001$).

cfPWV-age relationship was found to have a steeper increase in ESRD patients than in control subjects ($p < 0.05$), indicating the presence of EVA syndrome in these

Table 1. Hemodynamic, biochemical and arterial parameters for ESRD patients and control subjects

	Control (healthy) group	ESRD group	p value
Female, n (%)	283 (45)	151 (47)	0.875
Time of hemodialysis, months	59.2±11.3	54±50	
Age, years	1.69±0.10	57.8±15.9	0.294
Height, m	78.78±15.73	1.63±0.10	0.000
Body weight, kg	27.27±4.54	68.38±13.64	0.000
BMI, kg/m^2	126±12	25.62±4.57	0.083
SBP, mm Hg	90±9	124±16	0.212
MBP, mm Hg	74±9	89±17	0.354
DBP, mm Hg	67±10	72±14	0.456
Heart rate, beats/min	–	86±16	0.000
Hemoglobin, g/dl	–	10.55±1.83	–
Hematocrit, %	–	33.15±5.39	–
Serum albumin, g/dl	–	3.97±0.36	–
Calcium, mg/dl	–	8.98±1.07	–
Phosphates, mg/dl	–	4.82±1.02	–
Parathyroid hormone, pg/ml	–	398.41±392.87	–
Serum urea, mg/dl	–	140.92±36.02	–
Total cholesterol, mg/dl	211.34±41.29	182.36±45.98	0.000
HDL cholesterol, mg/dl	52.20±12.40	40.97±12.20	0.000
LDL cholesterol, mg/dl	132.93±37.25	109.58±38.25	0.000
Total triglycerides, mg/dl	132.39±86.11	171.46±102.90	0.000
CV disease risk (10 years; FRS; %)	17.41±8.46	17.56±13.30	0.767
CV disease risk (10 years; BNF; %)	13.95±7.11	14.45±11.85	0.749
cfPWV, m/s	9.39±1.86	11.74±3.59	0.000
βPWV	1.93±0.78	3.36±1.99	0.000
$cfPWV_{T,}$ m/s	9.79±0.89	9.66±1.61	0.305
PWV_{Index}, m/s	–0.40±1.54	2.08±3.12	0.000

BMI = Body mass index; CV = cardiovascular. PWV index: absolute difference between measured and theoretical PWV ($PWV_{Index} = PWV_M - PWV_T$).

patients (table 2). This finding is evident in figure 2a, in which the comparison between both gradients shows a significant difference ($p < 0.05$). A similar finding was confirmed when βPWV was used (fig. 2b).

Analysis of ESRD Etiologies

Tables 2 and 3 show data obtained from ESRD hemodialysed patients included in table 1, discriminated by the pathology that led to the end stage of kidney failure and that which determined renal replacement therapy. As seen in table 2, chronic glomerulonephritis was the only etiology whose cfPWV-Age relationship was non-significant.

As seen in figure 3a, the highest cfPWV values were obtained from ESRD patients; among these values, values related to diabetic nephropathy and nephroangiosclerosis were the determinants of the kidney failure. These differences remained when PWV values were normalized with respect to pressure values obtained by calculating the βPWV (fig. 3b) and when the PWV_{Index} was calculated considering age, gender, heart rate and BP (fig. 3c).

Differences among etiological subgroups were characterized through regression analysis of cfPWV-age relationship of ESRD hemodialysed patients (table 2). The results showed statistically significant linear correlations for all groups with the only exception of chronic glomerulonephritis patients, for whom there was lack of statistical significance. As seen, comparing the gradients (slopes) showed differences among ESRD etiologies. Again, diabetic patients exhibit the most important EVA, since the gradient of the cfPWV-age relationship was the highest.

Hemodialysis Effects Analysis

As seen in table 4, data were obtained at 2 different points in time: time 1 (year 2007) and time 2 (year 2012). Significant differences (reported previously by Cabrera Fischer et al. [21]) were found in terms of cfPWV. Moreover, the calculation of βPWV and PWV_{Index} demonstrat-

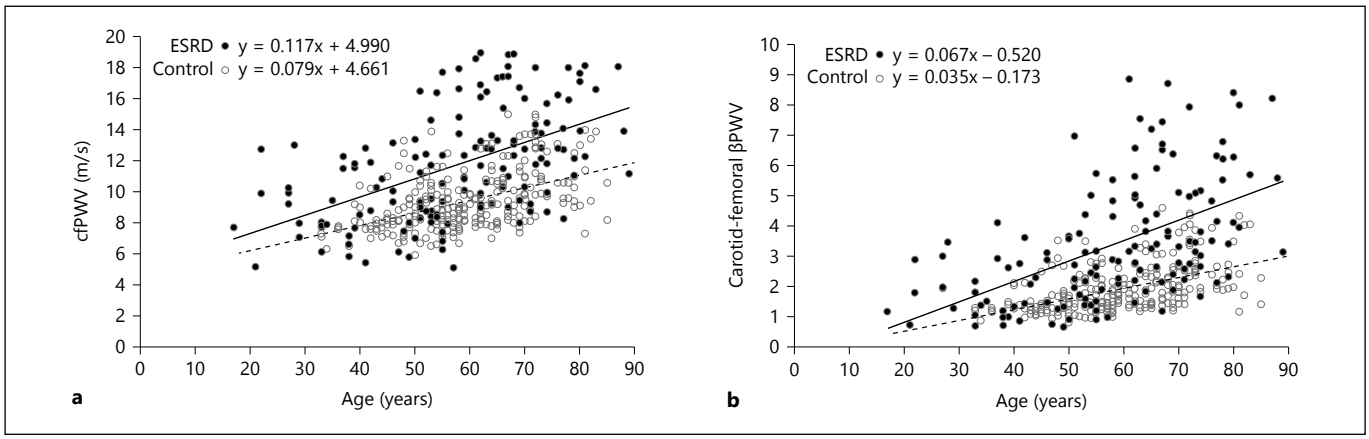

Fig. 2. a Relationship between age and the cfPWV of healthy (control) subjects ($p < 0.05$) and ESRD hemodialyzed patients ($p < 0.05$). The gradient (slope) of the ESRD group was higher than that observed in the control group ($p < 0.05$). **b** Relationship between age and the carotid-femoral stiffness index (βPWV) of healthy (control) subjects ($p < 0.05$) and ESRD hemodialyzed patients ($p < 0.05$). The gradient (slope) of the ESRD group was higher than that observed in the control group ($p < 0.05$).

Table 2. Regression equations (cfPWV vs. age) for control subjects and ESRD patients: etiological analysis

	R	Linear equation (PWV, m/s)	p value for each equation	Comparison of the slope (β)
ESRD and vascular aging				
Control group	0.5084	PWV = 4.661+0.0790 * age	0.000	
ESRD (entire group)	0.5592	PWV = 4.990+0.1174 * age	0.000	a
ESRD etiology and vascular aging				
Diabetic nephropathy	0.4587	PWV = 0.010+0.2039 * age	0.012	a, b
Unknown causes	0.5089	PWV = 5.912+0.1014 * age	0.003	a, c
Chronic glomerulonephritis	0.4022	PWV = 6.513+0.0770 * age	0.064	b, c
Tubulo-interstitial nephritis	0.9719	PWV = 0.634+0.2026 * age	0.006	a, b, d, e
Nephroangiosclerosis	0.4326	PWV = 3.956+0.1256 * age	0.032	a, c, f
Other causes	0.6743	PWV = 0.328+0.1743 * age	0.033	a, b, d
Polycystic renal disease	0.527	PWV = 1.103+0.1953 * age	0.036	a, b, d, e, g
Hemodialysis and vascular aging				
Time 1 (year: 2007)	0.631	PWV = 5.936+0.1314 * age	0.0243	a, c, e, f, h, i
Time 2 (year: 2012)	0.642	PWV = 4.759+0.0863 * age	0.0222	c, f, h, i, *

[a] $p < 0.05$ with respect to control group.
[b] $p < 0.05$ with respect to ESRD (entire group).
[c] $p < 0.05$ with respect to diabetic nephropathy.
[d] $p < 0.05$ with respect to unknown causes.
[e] $p < 0.05$ with respect to chronic glomerulonephritis.
[f] $p < 0.05$ with respect to tublo-interstitial nephritis.
[g] $p < 0.05$ with respect to nephroangiosclerosis.
[h] $p < 0.05$ with respect to other causes.
* $p < 0.05$ with respect to time 1 (year: 2007).

ed statistically significant decreases of both parameters after the 5-year follow-up period ($p < 0.001$).

Regression analysis demonstrated a significant reduction of the gradient (slope) of cfPWV-age relationship between measurements performed in 2007 with respect to those measured in 2012 ($p < 0.05$; table 3). This change, observed in chronically hemodialized patients during the 5-year follow-up period, can also be visualized in figure 4a. Similarly, βPWV-age comparison of time 1 and time 2 showed a significant decrease after 5 years ($p < 0.05$) (fig. 4b).

Blood Purif 2017;43:18–30
DOI: 10.1159/000448986

Table 3. Hemodynamic, biochemical and arterial parameters for ESRD patients: etiological analysis

	Diabetic nephropathy	Unknown causes	Chronic glomerulonephritis	Tubulo-interstitial nephritis	Nephroangiosclerosis	Other causes	Polycystic renal disease
Female, n (%)	35 (43)	33 (42)	23 (65)	5 (60)	25 (48)	10 (40)	16 (38)
Time of hemodialysis, months	33±33	54±43[a]	61±65[a]	62±47[a]	65±59[a]	58±49[a]	68±52[a]
Age, years	63.3±9.9	52.7±18.2[a]	48.8±15.9[a]	43.8±22.9[a]	68.5±10.7[c, d]	63.5±12.0	58.8±10.4
Height, m	1.62±0.08	1.65±0.09	1.62±0.10	1.61±0.17	1.61±0.09	1.61±0.10	1.70±0.09[a–f]
Body weight, kg	69.19±13.65	68.27±14.50	64.11±12.80	66.90±15.42	67.90±10.79	66.91±10.78	76.28±17.39[a–f]
BMI, kg/m^2	26.45±5.13	25.00±4.56	24.54±4.64	25.63±4.08	26.34±4.19	25.75±3.82	26.24±4.17
SBP, mm Hg	125±31	134±20[a]	125±29[b]	100±18[a–c]	117±22[b, d]	118±23[b, d]	121±25[b, d]
MBP, mm Hg	88±18	97±14[a]	89±20[b]	75±12[a–c]	85±13[b, d]	86±16[b, d]	89±18[b, d]
DBP, mm Hg	70±14	79±12[a]	71±19	62±11[a–c]	69±12[b, d]	70±15[b, d]	72±15[b, d]
Heart rate, beats/min	84±14	85±13	83±24	89±14	91±16	96±19[a–d]	84±13[f]
Hemoglobin, g/dl	10.35±1.95	10.02±1.74	10.57±1.69	10.04±2.78	10.45±2.04	11.32±1.00	11.68±1.47
Hematocrit, %	32.97±5.14	31.33±5.24	33.16±5.09	31.76±8.04	32.91±6.50	35.40±3.43	36.51±4.44[b]
Serum albumin, g/dl	3.84±0.37	3.97±0.37	4.09±0.43	3.91±0.60	3.95±0.29	4.05±0.22	3.98±0.31
Calcium, mg/dl	8.70±0.58	9.06±0.73	9.37±1.28	7.52±4.30[c]	8.97±0.61	9.02±0.43	9.10±0.51
Phosphates, mg/dl	4.79±0.85	4.94±0.98	5.03±0.74	4.46±2.67	4.46±1.13	4.69±0.86	4.98±0.98
Parathyroid hormone, pg/ml	324.37±261.42	427.10±312.36	508.15±566.45	192.70±317.64	343.56±333.57	491.67±279.16	488.80±602.71
Serum urea, mg/dl	133.47±35.54	148.85±42.26	141.87±33.76	135.20±17.63	132.32±32.64	136.70±38.38	150.81±33.90
Total cholesterol, mg/dl	175.50±57.73	179.48±51.07	184.30±34.01	187.80±43.29	190.56±45.30	190.70±38.08	178.94±27.99
HDL cholesterol, mg/dl	40.15±10.95	42.30±15.08	40.30±11.93	39.20±10.55	43.28±9.03	42.80±12.47	36.38±8.56
LDL cholesterol, mg/dl	103.12±41.27	106.85±41.07	114.67±28.75	113.12±19.81	115.73±35.70	108.56±58.17	106.40±27.04
Total triglycerides, mg/dl	175.44±99.67	175.83±135.83	159.11±80.05	177.00±159.89	149.96±68.01	174.40±114.71	190.75±72.75
CV disease risk (10 years; FRS; %)	26.84±15.84	13.52±11.91[a]	11.63±9.16[a]	8.09±8.95	21.50±11.47[b–d]	14.74±11.56[a, d, e]	16.05±8.93[a, d, e]
CV disease risk (10 years; BNF; %)	22.31±15.23	10.98±10.31[a]	10.00±7.90[a]	5.15±5.35	17.32±10.56[b–d]	12.57±9.73[a, d, e]	13.21±6.79[a, d, e]
cfPWV$_T$, m/s	10.16±0.96	9.67±1.36	8.49±2.46[a]	7.98±2.10[a]	10.43±1.19[c, d]	10.14±0.91[c, d]	9.79±1.09[d]

BMI = Body mass index; CV = cardiovascular. PWV$_T$ expected using Blacher et al. model [28].
[a] $p < 0.05$ with respect to diabetic Nephropathy.
[b] $p < 0.05$ with respect to unknown causes.
[c] $p < 0.05$ with respect to chronic glomerulonephritis.
[d] $p < 0.05$ with respect to tublo-interstitial nephritis.
[e] $p < 0.05$ with respect to nephroangiosclerosis.
[f] $p < 0.05$ with respect to polycystic renal disease.

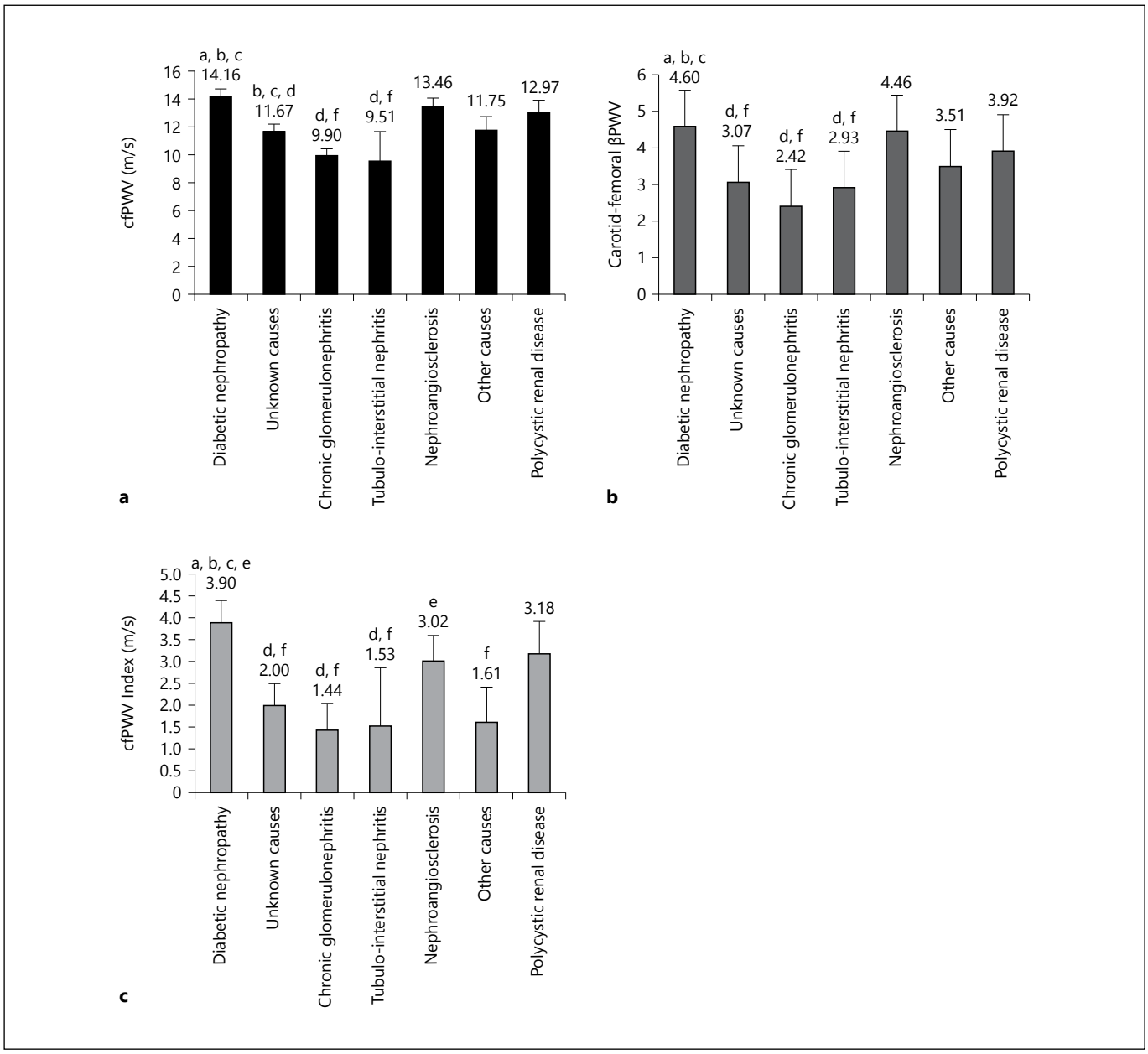

Fig. 3. a cfPWV and pathologies that determine kidney failure in the hemodialyzed patents included in this research (n = 151). ANOVA followed by Bonferroni test shows: [a] $p < 0.05$ with respect to unknown causes. [b] $p < 0.05$ with respect to chronic glomerulonephritis. [c] $p < 0.05$ with respect to tubulo-interstitial nephritis. [d] $p < 0.05$ with respect to nephroangiosclerosis. [e] $p < 0.05$ with respect to other causes. [f] $p < 0.05$ with respect to polycystic renal disease. **b** βPWV and pathologies that determine kidney failure in the hemodialyzed patents included in this research (n = 151). ANOVA followed by Bonferroni test shows: [a] $p < 0.05$ with respect to unknown causes. [b] $p < 0.05$ with respect to chronic glomerulonephritis. [c] $p < 0.05$ with respect to tubulo-interstitial nephritis. [d] $p < 0.05$ with respect to nephroangiosclerosis. [e] $p < 0.05$ with respect to other causes. [f] $p < 0.05$ with respect to polycystic renal disease. **c** PWV_{Index} and pathologies that determine kidney failure in the hemodialyzed patents included in this research (n = 151). ANOVA followed by Bonferroni test shows: [a] $p < 0.05$ with respect to unknown causes. [b] $p < 0.05$ with respect to chronic glomerulonephritis. [c] $p < 0.05$ with respect to tubulo-interstitial nephritis. [d] $p < 0.05$ with respect to nephroangiosclerosis. [e] $p < 0.05$ with respect to other causes. [f] $p < 0.05$ with respect to polycystic renal disease.

Table 4. Hemodynamic, biochemical and arterial parameters for ESRD patients under hemodialysis: 5-years follow-up

	ESRD, time 1	ESRD, time 2	p value, time 1 vs. time 2
Female, n (%)	25 (36)	25 (36)	1.000
Time of hemodialysis, months	62±43	118±44	0.000
Age, years	53.9±15.9	59.2±15.9	0.000
Height, m	1.66±0.09	1.61±0.10	0.000
Body weight, kg	68.7±12.0	67.3±12.1	0.297
BMI, kg/m^2	25.03±4.10	25.96±3.53	0.169
SBP, mm Hg	129±25	121±26	0.149
BP, mean, mm Hg	92±17	88±15	0.269
DBP, mm Hg	74±14	71±12	0.491
Heart rate, beats/min	85±12	85±12	0.961
Hemoglobin, g/dl	10.24±1.82	11.12±1.43	0.024
Hematocrit, %	31.69±5.77	35.68±4.29	0.001
Serum albumin, g/dl	3.96±0.44	3.92±0.32	0.662
Calcium, mg/dl	9.17±0.58	8.86±0.48	0.003
Phosphates, mg/dl	5.00±1.13	4.55±0.84	0.035
Parathyroid hormone, pg/ml	479.01±559.70	411.00±358.12	0.607
Serum urea, mg/dl	149.80±43.79	145.96±39.27	0.669
Total cholesterol, mg/dl	181.00±46.29	170.96±58.50	0.323
HDL cholesterol, mg/dl	38.00±9.45	42.28±10.52	0.013
LDL cholesterol, mg/dl	111.76±42.60	99.04±49.31	0.095
Total triglycerides, mg/dl	198.92±117.08	158.00±77.35	0.045
CV disease risk (10 years; FRS; %)	17.45±12.99	41.94±9.28	0.006
CV disease risk (10 years; BNF; %)	14.46±11.97	9.43±7.33	0.004
cfPWV, m/s	13.27±2.96	9.75±2.99	0.000
βPWV	4.09±1.52	2.28±1.08	0.000
$cfPWV_T$, m/s	9.77±1.24	9.81±1.46	0.225
PWV_{Index}, m/s	3.67±2.09	0.02±1.74	0.000

BMI = Body mass index; CV = cardiovascular. PWV_T expected using Blacher et al. model [28]. PWV index: absolute difference between measured and theoretical PWV ($PWV_{Index} = PWV_M - PWV_T$).

Finally, no significant association was found between BP changes and arterial stiffness variations (PWV or βPWV) in the course of the 5-year follow-up period (table 5).

Discussion

The relationship between ESRD patients and arterial stiffness has been largely analyzed. Recently, London et al. [29] showed that a significantly steeper age-aortic PWV correlation (i.e. accelerated age-related changes of aortic stiffness) was observed in ESRD patients when they were compared with their matched control group in terms of age, gender, and MBP, but not when compared with cardiovascular risk factors. Additionally, London et al. [29] showed that brachial (or femoral) arterial stiffness remains almost stable throughout aging, and consequently the changes in the central-to-peripheral arterial stiffness gradient (a proposed independent index of ESRD survival) depend entirely on aortic PWV changes. The accelerated changes of aortic stiffness observed in ESRD patients is detrimental per se (i.e. by increasing the left ventricle afterload), and could determine a premature and detrimental reduction (or even inversion) of the central-to-peripheral arterial stiffness, which in turn could provoke several hemodynamic perjuries at the microcirculation and heart level (i.e. increased wave reflections). However, in the mentioned works, the groups were not matched in terms of cardiovascular risk factors exposition and the ESRD groups were considered a homogeneous cohort without any evaluation of possible etiology-dependent differences. Consequently, no analysis was performed to elucidate whether the arterial stiffness increases related to

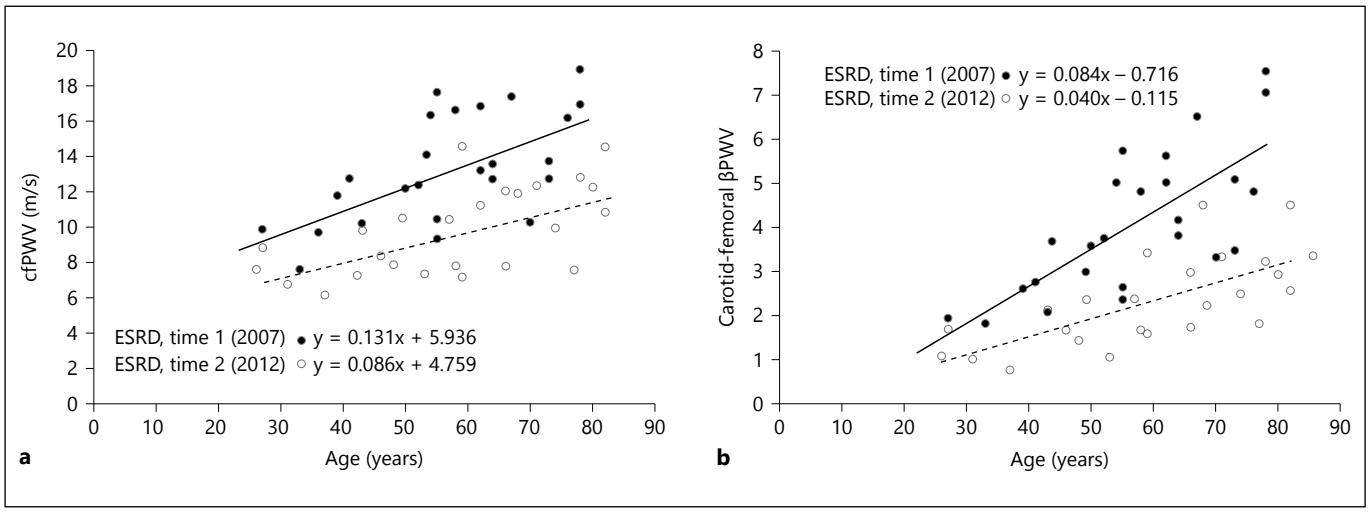

Fig. 4. a Relationship between age and the PWV_{Index} relationship of ESRD hemodialyzed patients obtained in the year 2007 (time 1, $p < 0.05$) and 5 years later (time 2, $p < 0.05$). The gradient (slope) of time 2 was lower than that observed in time 1 ($p < 0.05$). **b** Relationship between age and βPWV relationship of ESRD hemodialyzed patients obtained in the year 2007 (time 1, $p < 0.05$) and 5 years later (time 2, $p < 0.05$). The gradient (slope) of time 2 was lower than that observed in time 1 ($p < 0.05$).

Table 5. Mean levels and correlation analysis between differences in BP and stiffness levels: 5-years follow-up

	Mean ± SD	Correlations with respect to arterial stiffness differences		
			$PWV_{T2} - PWV_{T1}$	$\beta PWV_{T2} - \beta PWV_{T1}$
$PWV_{T2} - PWV_{T1}$, m/s	–3.3±2.6	Pearson correlation	1	0.857
		Sig. (2-tailed)	<0.001	<0.001
$\beta PWV_{T2} - \beta PWV_{T1}$	–1.6±1.3	Pearson correlation	0.857	1
		Sig. (2-tailed)	<0.001	<0.001
$SBP_{T2} - SBP_{T1}$, mm Hg	–8.2±27.5	Pearson correlation	0.296	–0.128
		Sig. (2-tailed)	0.151	0.541
$DBP_{T2} - DBP_{T1}$, mm Hg	–2.2±16.0	Pearson correlation	0.411	0.0001
		Sig. (2-tailed)	0.061	0.995
$PP_{T2} - PP_{T1}$, mm Hg	–6.0±18.4	Pearson correlation	0.085	–0.194
		Sig. (2-tailed)	0.686	0.354
$MBP_{T2} - MBP_{T1}$, mm Hg	–4.2±18.7	Pearson correlation	0.381	–0.062
		Sig. (2-tailed)	0.071	0.767

Subscripts T1 and T2 = parameter level in 2007 (time 1) and 2012 (time 2), respectively; sig. = statistical significance. A $p < 0.05$ was considered statistically significant.

the aging process were associated or independent of the pathology that determined the ESRD. Hypothetically, the acceleration of the aortic stiffness is not the same in all ESRD patients, and as such, this excludes any possibility of generalizing theories about this pathological process. Taking into account these facts, our research aimed to elucidate whether the acceleration of the aortic stiffness is associated with the kidney disease or if, on the contrary, it was homogeneous and independent of the etiology. Moreover, an important issue to study was the quantification of the aortic aging associated to hemodialysis. Previous reports of our group attempted to elucidate the effects of chronic renal replacement therapy (hemodialysis) on arterial stiffness, demonstrating a statistically significant improvement of aortic stiffness in a cohort of ESRD hemodialyzed patients [21]. However, to the best of our knowledge, no research on EVA and renal replacement therapy in hemodialyzed patients has been reported.

In the above-mentioned context, the results of our research are described taking into account findings in EVA analysis, differences in terms of pathologies determining ESRD and the effects of hemodialysis treatment on EVA.

EVA and ESRD

Patients in ESRD not only showed higher levels of aortic stiffness with respect to those exhibiting similar characteristics, such as age, gender and exposition to cardiovascular risk factors (table 1), but also exhibited an EVA, characterized by a steeper slope of the cfPWV-age and carotid-femoral βPWC-age relationship (fig. 2a, b; table 2). The latter is not a minor issue, since the comparison between hemodialyzed ESRD patients with healthy subjects did not show any statistically significant differences in terms of traditional risk factors. If the fact that cardiovascular disease is the most important cause of morbidity and mortality in chronically hemodialyzed patients (CHP) is given due consideration, then the use of the EVA concept provides a useful tool that allows the possibility of conducting a more integrative analysis of these patients. In this context, our results show that even after having weighed exposure to traditional risk factors, in order to match the level of risk determined by global cardiovascular risk equations (i.e. FRS and BNF), the ESRD population showed a vascular condition that was certainly worse than that in the control group. However, far from being a simple increase in the average levels of aortic stiffness, our results show, for the first time, that the differences between these groups increase with age, which clearly means that the vascular alterations in these ESRD hemodialyzed patients quickly progress to a remarkable EVA.

EVA and Renal Disease Etiology

Aortic stiffness levels (fig. 3a) and mainly EVA (table 2) differed in ESRD patients, depending on the etiology that determines their renal failure. The analysis helped in understanding that these differences remained greatly independent of factors like arterial BP (βPWV; fig. 3b) and from BP, age and gender of the patients (PWV_{Index}; fig. 3c). Among the etiologies, diabetic nephropathy and nefroangioeslcerosis were associated with higher levels of arterial stiffness. Furthermore, diabetic nephropathy showed a higher EVA increase among all the considered etiologies (table 2).

Taking into account the above-described results, it is noteworthy that the entire cohort of ESRDP patients included in this study is far from being a homogenous group in terms of EVA. From a clinical point of view, it is possible that patients with diabetic nephropathy could have an accelerated aortic stiffening process, but this is not the rule for other etiologies such as chronic glomerulonephritis, where patients show a similar arterial stiffness to the control group (table 2). These findings show that EVA is an etiology-dependent entity in ESRD patients and, according to our results, these patients would have differences in terms of left ventricular afterload and microcirculatory damage.

EVA and Hemodialysis

Renal replacement therapy resulted in a decrease in the rate of arterial aging, that is, an EVA reduction (table 2; fig. 4a, b), and also in a reduction of arterial stiffness, as seen in previous reports of our group [21]. This original finding shows an unknown effect of hemodialysis and may have clinical consequences on the most important cause of morbidity and mortality in ESRD patients: cardiovascular disease.

Some considerations should be made in order to understand the nature of the changes observed between evaluations conducted in 2007 and 2012, in light of the relationship between PWV, βPWV, and between PWV-age and βPWV-age. In this follow-up, no association between the mentioned variables and BP could be demonstrated (table 5) and at least 3 considerations should be made. First, the statistical analysis (paired t test, 2 tails) comparing year 2007 and year 2012 shows no significant differences in terms of BP, but remarkable differences in terms of PWV were observed (PWV; table 4). Second, these findings were accompanied by significant differences in terms of βPWV, a stiffness index with low dependence of BP levels (fig. 4). Third, the analysis of patient-to-patient differences showed no association in terms of BP between the 2007 and 2012 records and, on the contrary, changes in arterial stiffness were statistically significant (table 5).

There are 2 possible mechanisms responsible for the ESRD-associated PWV increase and the hemodialysis-related PWV decrease. The former is due to structural and the latter due to 'functional or passive' changes of the arterial wall. Structural stiffening of elastic arteries caused by aging and other cardiovascular risk factors is explained by the fragmentation and alteration of the elastic fiber network responsible for the buffering function of arteries and/or by arterial wall remodeling (i.e. increased collagen fiber synthesis) [26]. Functional stiffening of arteries results from increased BP. Under normal BP levels, the artery works in a pressure-diameter or stress-strain relationship mainly determined by the highly distensible elastic elastin fibers. Increased BP loads stiffen collagen

fibers, thereby increasing arterial stiffness in a passive way. This explains the nonlinear relationship between BP and PWV, and is the basis for βPWV calculation [25]. Functional or passive stiffening of arteries can be reversed by lowering the BP. In the presence of structural changes, the stiffening is less dependent on BP changes. Thus, changes in arterial stiffness would not be produced due to the increase in the systemic pressure; consequently, we can speculate that the observed improvement of aortic stiffness would not be associated with modifications in arterial BP. It is noteworthy that Guerin et al. [30] reported that the survival of patients with ESRD was significantly better for subjects whose aortic PWV declined in response to a decreasing BP compared to individuals without a PWV decrease after a BP decrease. In another study, individuals with an increased PWV before and after dialysis had an increased risk of death compared to subjects with an increased PWV before and normal PWV after dialysis [31]. In this context, at least theoretically, the observed decrease of PWV values associated to hemodialysis could be important in the reduction of cardiovascular risk of ESRD patients.

Clinical Aspects

The clinical connotations of this research are listed considering 3 different aspects. First, the demonstration of a significant increase of EVA in hemodialyzed patients with respect to control subjects is very important and it has therapeutical connotations. Indeed, renal replacement therapy very often increased the survival rates of ESRD patients; but this was not only due to the programmed hemodialysis sessions. On the contrary, the control of cardiovascular risk factors is involved in the mentioned observed survival improvement, since the very beginning of hemodialytic treatment.

With respect to the arterial stiffness differences found among the pathologies determining ESRD subgroups, this investigation is pointing out significant differences that should be taken into account in clinical practice. In this sense, according to our results, the fact that arterial impairment in diabetic and nephroangiosclerotic patients is higher than patients with chronic glomerulonephritis or tubulo-insterstitial nephritis should be considered. Hypothetically, these findings should have prognostic relevance. More investigations including a higher number of patients should be carried out in order to complete this result. To the best of our knowledge, there is lack of research on this important matter and the available reports are not conclusive regarding prognostic markers such as EVA quantification [32, 33].

Finally, the relevance of EVA evaluation in hemodialyzed patients along a 5-year follow-up shows complementary information that is in accordance with the aortic stiffness improvement, as previously reported by our group [21]. Future longitudinal studies should include EVA quantification in order to identify biomarkers of VA, as it was previously proposed [34]; they should be particularly directed to clarify the contradictory results observed in the literature about the effects of chronic hemodialysis on arterial stiffness [17].

Conclusion

Patients in ESRD showed higher levels of EVA, characterized by a steeper slope of the cfPWV-age and carotid-femoral βPWC-age relationship. Aortic stiffness levels and EVA differed in ESRD patients depending on the pathology that determined their renal failure. Moreover, these differences were independent of factors like arterial BP, age and gender of the analyzed patients. CHP showed an EVA reduction after the 5-year follow-up period.

Disclosure Statement

The authors declare that there are no conflicts of interest.

Financial Support

This work was supported by the René Favaloro University Foundation and funds from 'PICT 2008 OC AR 0340' (Argentina) and Agencia Nacional de Investigación e Innovación (ANII), Comisión Sectorial de InvestigaciónCientífica and Espacio Interdisciplinario (Republic University, Uruguay). Additionally, this work was supported by extrabudgetary funds generated by CUiiDARTE Centre and Project. Professor Dr. Yanina Zócalo and Professor Dr. Daniel Bia are the Directors of CUiiDARTE Centre and Project.

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