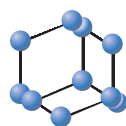


RESEARCH ARTICLE

BENTHAM
SCIENCE

Central-To-Peripheral Arterial Stiffness Gradient in Hemodialyzed Patients Depends on the Location of the Upper-limb Vascular Access



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Abstract: Background: Pulse wave velocity ratio (PWV-ratio), a measure of central-to-peripheral arterial stiffness gradient, is calculated as a quotient between carotid-femoral and carotid-radial PWV (cf-PWV/cr-PWV). This new index has been reported to be significantly associated with increased mortality in hemodialyzed patients. Since several reports showed differences in arterial stiffness regarding the pathway where the vascular access (VA) is, the purpose of this research was: a) to compare arterial stiffness values obtained in the left and right sides of the body in hemodialyzed and non-hemodialyzed patients, and b) to analyze PWV-ratio values obtained on the side of the body where the VA was placed and compare them to its contralateral intact side. Since it is difficult to adequately measure cr-PWV in patients with a VA in the forearm, we measured the carotid-brachial PWV (cb-PWV) and used it to calculate PWV-ratio (cf-PWV/cb-PWV).

Methods: A Pearson's correlation and Bland & Altman analysis were performed in hemodialyzed (n=135) and non-hemodialyzed (n=77) patients, to quantify the equivalence between arterial stiffness parameters (cf-PWV, cb-PWV, PWV-ratio) obtained on each side of the body with respect to its contralateral side.

Results: We conclude that PWV-ratio values measured on the side where the VA is placed were significantly higher than those obtained in its contralateral side, in hemodialyzed patients included in this research. Moreover, cf-PWV, cb-PWV and PWV-ratio values obtained on one side of the body were always highly correlated with its contralateral side.

Conclusion: According to this research, any research involving PWV-ratio should always consider the observed territory.

Keywords: Arterial stiffness, aortic stiffness, hemodialysis, pulse wave velocity, PWV-ratio, territory.

1. INTRODUCTION

Hemodialyzed patients are at high risk of cardiovascular disease, since the acceleration of arterial stiffening is associated to kidney disease and co-morbidities such as systemic hypertension, diabetes and arterial calcification in renal patients [1]. Aortic pulse wave velocity (PWV) proved to be the best prognostic marker of mortality and morbidity in end-stage renal disease patients [2]. Since this discovery, several indexes have been developed, in order to increase the

prognostic power of arterial stiffness measurements [3]. This strategy included the exploration of arterial stiffness in peripheral vessels; however, neither brachial nor femoro-tibial PWV showed to have prognostic value [4].

Despite this failed report by Pannier *et al.* [4], peripheral arterial stiffness was included in the calculation of a new index based on the quantification of the mismatch between carotid-femoral PWV (cf-PWV) and carotid-radial PWV (cr-PWV) or carotid-brachial PWV (cb-PWV).

This new index, PWV-ratio, is calculated as cf-PWV/cr-PWV, and was reported to be significantly associated with increased mortality in a cohort of hemodialyzed patients [5].

In 2016, London *et al.* reported an index to evaluate central and peripheral stiffness using the formula: (brachial

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PWV/aortic PWV)^{0.5} [6]. Additionally, the PWV-ratio developed by Fortier *et al.* was recently strongly associated with the extent of aortic arch calcification in hemodialyzed patients [7].

PWV-ratio, calculated as cf-PWV/cr-PWV, has not only been shown to be important as a predictor, but also to be independent of the blood pressure of the observed subjects, proving itself to be more powerful than cf-PWV [8]. However, the calculation of PWV-ratio should consider some methodological aspects, as reported by Bossuyt *et al.* [9] and by our group [10].

Bossuyt *et al.* took the well-known anatomical differences in the arterial tree and explored the carotid-femoral pathway, comparing the right and left sides of the body [9]. The right carotid artery branches off the common carotid trunk, while the left carotid artery branches off the aortic arch. This group showed that the right carotid femoral pathway is slightly longer than the left one [9]. As PWV-ratio is calculated using either the right or the left arterial pathway, the difference between both should be considered.

In 2015, our group reported that hemodialysis was associated with decreases of cf-PWV and cb-PWV along a 5-year follow-up study. Additionally, previous works by our group showed that cb-PWV in upper limbs with arterio-venous fistulae is significantly lower than in its contra-lateral arm (*i.e.* the arm without the vascular access (VA)) [10]. The following question should be posed: Does PWV of a hemodialyzed patient differ depending on whether it is measured in the upper limb with the VA or in the upper limb without the VA? We hypothesize that anatomical and functional differences determined by the arteriovenous fistulae can determine differences when calculating PWV-ratio in hemodialyzed patients.

1.1. Accordingly, the Aims of our Research were

- (1) To study a cohort of chronic kidney disease patients, and calculate PWV-ratio values using cf-PWV and cb-PWV values measured in both right and left sides of the body. These non-dialyzed patients have intact arteries in both carotid-radial pathways;
- (2) To analyze a cohort of hemodialyzed patients, calculating PWV-ratio values from PWV measured in the right and left sides of the body. These hemodialyzed patients have an arteriovenous fistula in either the right or left carotid-radial pathways;
- (3) To analyze PWV-ratio values calculated from cb-PWV and cf-PWV measured on the side of the body where the arteriovenous fistula is placed and compare them with measurements in the contralateral side (*i.e.* intact carotid radial pathway), in a cohort of hemodialyzed patients.

2. MATERIALS AND METHODS

This investigation includes two populations in which arterial stiffness was evaluated using the same technology and methodology. This study was approved by our Institutional Review Board and Ethics Committee. All patients gave their written consent.

2.1. Patient Selection

Ambulatory hemodialyzed patients (hemodialyzed cohort, n=135) from a single Center (Fresenius-Medical Care, Buenos Aires, Argentina), were included in this research. The inclusion criteria were: (1) patients were on hemodialysis for at least 3 months, (2) patients agreed to partake in this research, (3) patients were free of any cardiovascular disease during the 6 months prior to entering this investigation, (4) patients had a vascular access in one upper-limb, (5) patients had an intact contralateral limb, *i.e.* there are no previous unused vascular accesses in the arm opposite to the current vascular access. The exclusion criteria were: (1) alcohol abuse, (2) unwillingness to partake in this investigation, (3) symptomatic cardiovascular disease, (4) patients with amputated lower- or upper-limbs, (5) uncontrolled diabetes mellitus, (6) uncontrolled hypertension (average brachial systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg) in the last three months. All patients included in this group were hemodialyzed three times a week during four to five hours on a standard bicarbonate bath. During each hemodialysis session, clinical data were routinely monitored, including: body height, brachial blood pressure, body temperature, heart rate and pre- and post-dialysis dry body weight. Th hemodynamic, anthropometric and arterial data of all patients were recorded before their scheduled midweek dialysis.

Chronic kidney disease ambulatory patients (non-hemodialyzed cohort, n=77) were selected from the Nephrology and Dialysis Unit of the Santojanni Hospital (Buenos Aires, Argentina). The inclusion criteria were: (1) non-dialyzed patients with chronic kidney disease, (2) agreement to partake in this research, (3) no cardiovascular disease during the 6 months prior to entering this investigation. The exclusion criteria were: (1) alcohol abuse, (2) unwillingness to partake in this investigation, (3) symptomatic cardiovascular disease, (4) lower or upper extremity amputation, (5) uncontrolled diabetes mellitus, (6) uncontrolled hypertension (average brachial SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) in the last three months. The evaluation process included a medical interview, laboratory measurements and non-invasive cardiovascular evaluation. Hemodynamic, anthropometric and arterial data were recorded during programmed routine medical controls.

2.2. Study Design and Data Acquisition

In this cross-sectional study, non-dialyzed and hemodialyzed patients were evaluated in a single data acquisition session in which arterial stiffness (cf-PWV and cb-PWV) was measured in the right and left sides of the body. All data was acquired by a single researcher, using the same techniques and equipment. Furthermore, other physical parameters (blood pressure, heart rate, height and body weight) were recorded. Blood samples were drawn in a fasting state according to routine biochemical laboratory protocols, to measure hematocrit, hemoglobin, serum urea, calcium, phosphate, albumin, total cholesterol, HDL and LDL cholesterol and triglycerides levels. In hemodialyzed patients, brachial blood pressure was measured in the upper-limb with no VA. In both chronic kidney disease (*i.e.* non-hemodialyzed)

and hemodialyzed patients, blood pressure was measured after resting in a supine position for 15 minutes with a digital automatic monitor (HEM 781INT, Omron Healthcare, Kyoto). Dyslipidemia was defined as total cholesterol >5.17 mmol/l (199 mg/dl) or Triglycerides >1.7 mmol/l (149 mg/dl). Systemic hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

cf-PWV was measured by recording carotid and femoral artery pressure waveforms. Data was acquired keeping the patient in a supine position, using high-fidelity mechano-transducers simultaneously placed on the skin over the carotid and femoral arteries (Arteriometer, Model V100, Oxytech, Buenos Aires, Argentina). After adequate pulse waveforms were obtained during a period of 30 seconds, digitization was suspended and the carotid-femoral propagation time (Δt) was calculated as the temporal foot-to-foot difference between the carotid and femoral pressure waveforms of corresponding cardiac cycles. The distance between carotid and femoral recording sites (Δx) was then measured using a measuring tape over the body surface. PWV was automatically calculated as the quotient between Δx and Δt , according to the technique widely used by our group and previously reported [10-13]. The PWV reported value for each patient is the average of three consecutive recordings. PWV in the upper limb (cb-PWV) was measured by placing mechano-transducers in the carotid and in the brachial arteries. In hemodialyzed patients, the latter was placed in the brachial artery proximal to the arteriovenous fistula. Since it is difficult to adequately measure cr-PWV in patients with a VA in the forearm, in this work we measured the carotid-brachial PWV (cb-PWV) and used it to calculate PWV-ratio (cf-PWV/cb-PWV).

In each subject, cf-PWV and cb-PWV were calculated in both the right and the left sides of the body (cf-PWV right, cf-PWV left, cb-PWV right, cb-PWV left, respectively). Next, we calculated the average cf-PWV as: (cf-PWV right + cf-PWV left)/2. PWV-ratio in the right side was: average cf-PWV/cb-PWV right and in the left side as average cf-PWV/cb-PWV left. Similar calculi were performed when the body side with the VA and the contralateral (without VA) were considered [8].

2.3. Statistical Analysis

Data were reported as mean value \pm standard deviation for all variables after a normal distribution was confirmed.

A Pearson's correlation and Bland & Altman analysis were performed in hemodialyzed and non-hemodialyzed patients to quantify the equivalence between arterial stiffness parameters (cf-PWV, cb-PWV, PWV-ratio) obtained in each side of the body with its contralateral side. In hemodialyzed patients a similar analysis was followed to study the equivalence between stiffness parameters obtained on the side of the body where the VA was placed with its contralateral intact side. R (Pearson's correlation parameter) and p values were obtained to quantify the degree of correlation between variables. Bland & Altman analysis was used to check the existence of systematic and proportional errors and intervals of confidence 95%. Mountain plots were used to facilitate the visualization of relative distribution among paired values.

Analyses were performed with SPSS 20.0 software (SPSS, Chicago, Ill., USA) and MedCalc 14.8 (MedCalc Software, Acaciaaan 22, B-8400 Ostend, Belgium). A $p < 0.05$ was regarded as statistically significant.

3. RESULTS

Data was successfully collected in chronic kidney disease (non-hemodialyzed) and hemodialyzed patients included in this study, according to the above-described routine methods followed by the research team. A unique arteriovenous shunt was confirmed in each hemodialyzed patient included in this study, in the right or left upper limb vessels, made up by arteries and veins of the forearm or in the distal third of the arm.

Table 1 shows data obtained from chronic kidney disease (non-hemodialyzed cohort) and hemodialyzed patients.

As seen in Tables 1 and 2, the arterial stiffness values for non-hemodialyzed patients show non-significant differences in terms of cf-PWV, cb-PWV and PWV-ratio when comparing both sides of the body. Pearson's high correlation values were obtained for the same parameter between the right and the left sides of the body: cf-PWV ($R=0.876$), cb-PWV ($R=0.902$) and PWV-ratio ($R=0.918$). Moreover, no systematic or proportional error was found in the observed variables (Table 2). Summarizing, chronic kidney disease patients (non-hemodialyzed) showed no differences between both body sides in terms of arterial stiffness parameters.

Similar results to those found in non-hemodialyzed subjects were observed in the hemodialyzed cohort in terms of cb-PWV and PWV-ratio values, when right and left arterial stiffness parameters were analyzed (Tables 1 and 3). Moreover, cf-PWV values calculated in the right body side were significantly higher than those obtained in the left side (mean or systematic difference or error 0.30 m/s; $p < 0.05$). See Tables 1 and 3.

As in non-hemodialyzed patients, the hemodialyzed cohort showed high Pearson's correlation values: cf-PWV right vs. cf-PWV left ($R=0.929$); cb-PWV right vs. cb-PWV left ($R=0.602$); PWV-ratio right vs. PWV-ratio left ($R=0.634$); cb-PWV in the upper limb with the vascular access vs. cb-PWV in upper limb without the access ($R=0.617$) and PWV-ratio on the side with the vascular access vs. PWV-ratio in the contralateral intact side ($R=0.651$). All correlations were significant ($p < 0.01$).

In the hemodialyzed cohort, cb-PWV values obtained in the upper-limb with the vascular access were lower than those measured in the contralateral intact arterial pathway (despite of a non-significant p value), particularly when cb-PWV values were lower (slope or proportional error 0.2487; $p < 0.005$, Table 3). Moreover, PWV-ratio values calculated on the side of the body where the vascular access was placed were significantly higher than those observed in its contralateral intact arterial pathways (mean or systematic difference or error = 0.05977; $p < 0.05$).

Figs. 1 to 5 show that, in hemodialyzed patients, each arterial stiffness parameter calculated on one side of the body, was positively correlated with its contralateral side,

Table 1. Characteristics of renal disease patients.

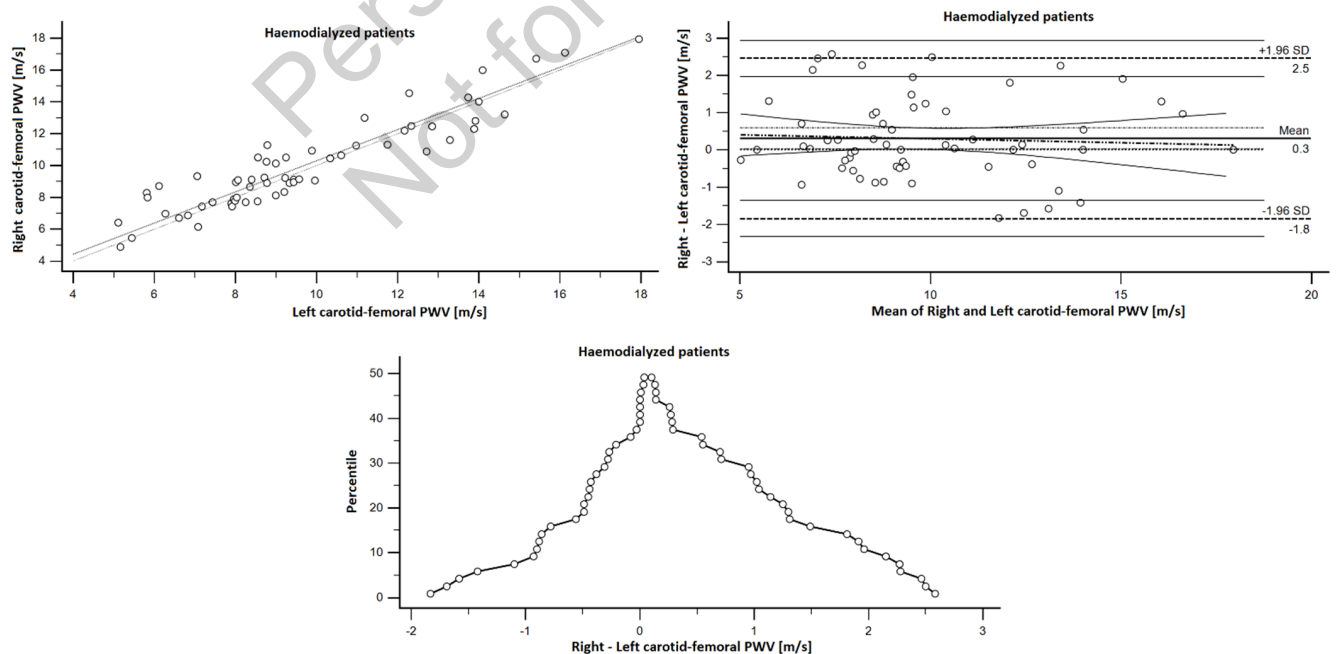
		Non-hemodialyzed Patients (n=77)				Hemodialyzed Patients (n=135)			
		MV or %	SD	Min.	Max	MV or %	SD	Min.	Max
Clinical Parameters	Time of hemodialysis [month]	-----	-----	-----	-----	54.897	49.9113	1	222
	Age [years]	68.89	12.79	33.54	89.31	57.91	15.94	17.00	89.00
	Sex, Female [%]	58.1%				47.3%			
	Bodyweight [Kg.]	65.06	18.66	52	89.70	68	14	41	119
	Bodyheight [cm]	157.0	25.0	136.,2	185.00	163.3	16.7	138.5	184.5
	SBP [mmHg]	141	30	95	219	124	26	93	190
	MBP [mmHg]	98	20	66	153	89	17	65	138
	DBP [mmHg]	79	15	45	114	72	15	46	124
	HR [beats/minute]	74	15	54	135	87	15	52	143
	Total Cholesterol [mg/dl]	173	39	94	249	182	46	101	379
	HDL Cholesterol [mg/dl]	44	15	21	106	41	12	19	81
	LDL Cholesterol [mg/dl]	105	42	44	306	109	37	16	249
	Triglycerides [mg/dl]	121	57	49	345	171	104	0	630
	Serum urea [g/l]	56	30	14	150	141	36	70	247
	Serum albumin [g/dl]	3.90	0.46	2.60	4.80	3.97	.36	2.93	4.90
	Serum calcium (mg/dl)	9.34	0.54	7.90	10.90	8.98	1.08	0.70	13.60
	Hematocrit [%]	38.9	4.4	28.1	49.0	33.3	5.3	12.1	46.2
	Hemoglobin [g/dl]	12.8	1.9	6.2	17.0	10.6	1.8	4.0	14.5
	Hypertension [%]	86.4				92.2			
	Dyslipidemia [%]	80.7				82.4			
	Diabetes [%]	37.4				25.7			
Arterial Parameters	carotid-femoral PWV Right [m/s]	14.2	3.2	6.8	18.8	12.1	3.2	4.9	18.0
	carotid-femoral PWV Left [m/s]	14.3	3.0	6.6	19.1	11.8	3.6	5.1	19.0
	carotid-femoral PWV Average [m/s]	14.2	2.9	6.7	18.7	12.0	3.5	5.0	19.0
	carotid-brachial PWV Right [m/s]	10.4	1.9	4.9	15.1	9.0	2.7	3.9	18.5
	carotid-brachial PWV Left [m/s]	10.0	2.2	4.5	13.5	9.3	3.0	3.7	18.4
	PWV Ratio Right	1.37	0.35	0.73	2.64	1.33	0.39	0.68	2.68
	PWV Ratio Left	1.42	0.48	0.91	3.22	1.29	0.42	0.64	2.77
	carotid-brachial PWV without VA [m/s]	-----	-----	-----	-----	9.2	2.6	4.3	16.6
	carotid-brachial PWV with VA [m/s]	-----	-----	-----	-----	9.0	3.2	3.7	18.5
	PWV Ratio without VA	-----	-----	-----	-----	1.30	0.37	0.69	2.40
	PWV Ratio with VA	-----	-----	-----	-----	1.35	0.43	0.64	2.68

MV: mean value. SD: standard deviation. Min. and Max: minimal and maximal value. HR: heart rate. PWV: pulse wave velocity. VA: vascular access. SBP, MBP and DBP: systolic, mean and diastolic blood pressure.

Table 2. Bland & Altman analysis information: carotid-femoral and carotid-brachial PWV and PWV ratio in non-hemodialyzed patients.

	Carotid-femoral PWV [Reference: Right Side]	Carotid-brachial PWV [Reference: Right Side]	PWV Ratio [Reference: Right Side]
Mean error	-0.0440	0.3598	-0.0497
95% C.I.	-0.4861 / 0.3981	-0.0111 / 0.7309	-0.1381 / 0.0386
P*	0.8432	0.0571	0.2651
SD	1.8814	1.5093	0.3565
Lower Limit	-3.7316	-2.5984	-0.7485
95%C.I.	-4.4906 / -2.9725	-3.2357 / -1.9611	-0.9002 / -0.5967
Upper Limit	3.6435	3.3181	0.649
95% C.I.	2.8844 / 4.4026	2.6808 / 3.9554	0.4973 / 0.8008
Equation	$y = -1.553 + 0.108x$	$y = 1.509 + 0.114x$	$y = -0.186 + 0.096x$
Intercept			
Coefficient	-1.5535	1.5096	-0.1861
SE	1.0759	1.0746	0.2042
t-value	-1.4439	1.4047	-0.9112
P	0.1532	0.1649	0.3657
95% CI	-3.6993 / 0.5924	-0.6373 / 3.6564	-0.5942 / 0.2220
Slope			
Coefficient	0.1083	-0.1146	0.09625
SE	0.07558	0.1055	0.1407
t-value	1.4333	-1.0862	0.6841
p value	0.1562	0.2815	0.4964
95% C.I.	-0.04241 / 0.2591	-0.3255 / 0.09620	-0.1849 / 0.3774

PWV: pulse wave velocity. C.I.: confidence interval. SE and SD: standard error and deviation. $p < 0.05$ was considered statistically significant. *(H_0 : Mean error=0).

**Fig. (1).** Left upper panel: left and right carotid-femoral pulse wave velocity (PWV) correlation study in hemodialyzed patients (n=135). Right upper panel and bottom panel: Bland & Altman analysis and Mountain plot allow to visualize data used in the correlation study.

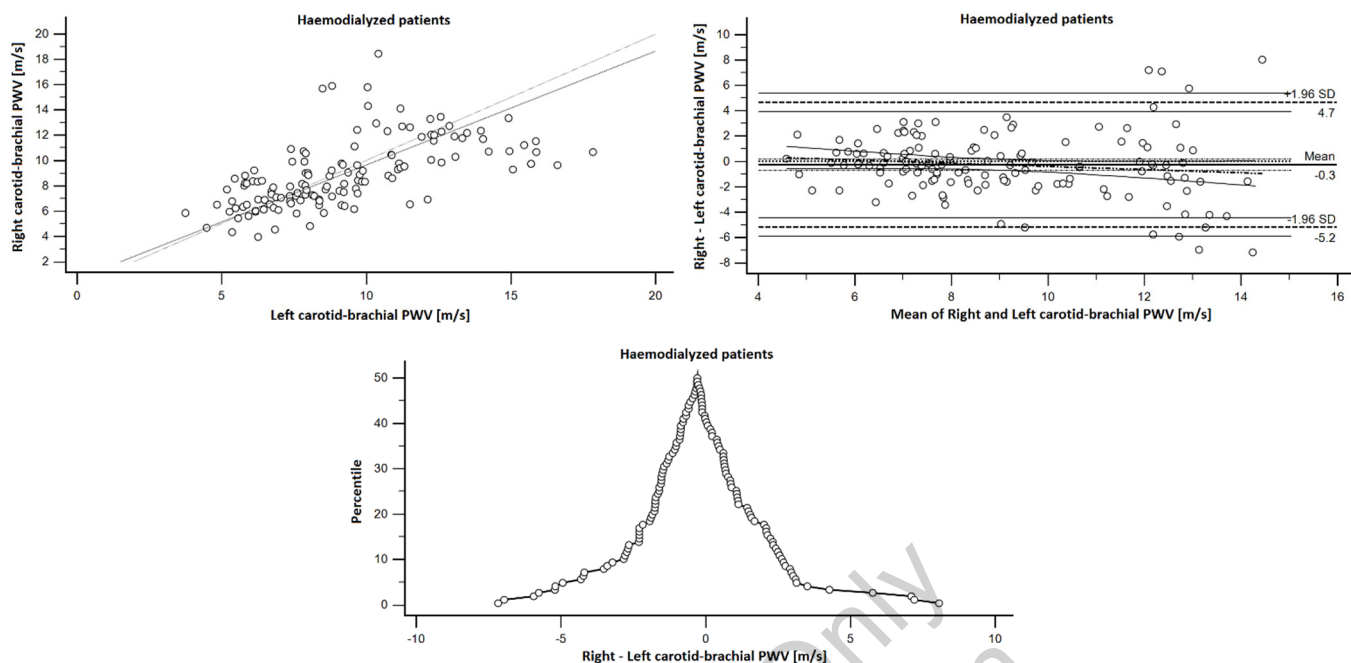


Fig. (2). Left upper panel: left and right carotid-brachial pulse wave velocity (PWV) correlation study in hemodialyzed patients (n=135). Right upper panel and bottom panel: Bland & Altman analysis and Mountain plot allow to visualize data used in the correlation study.

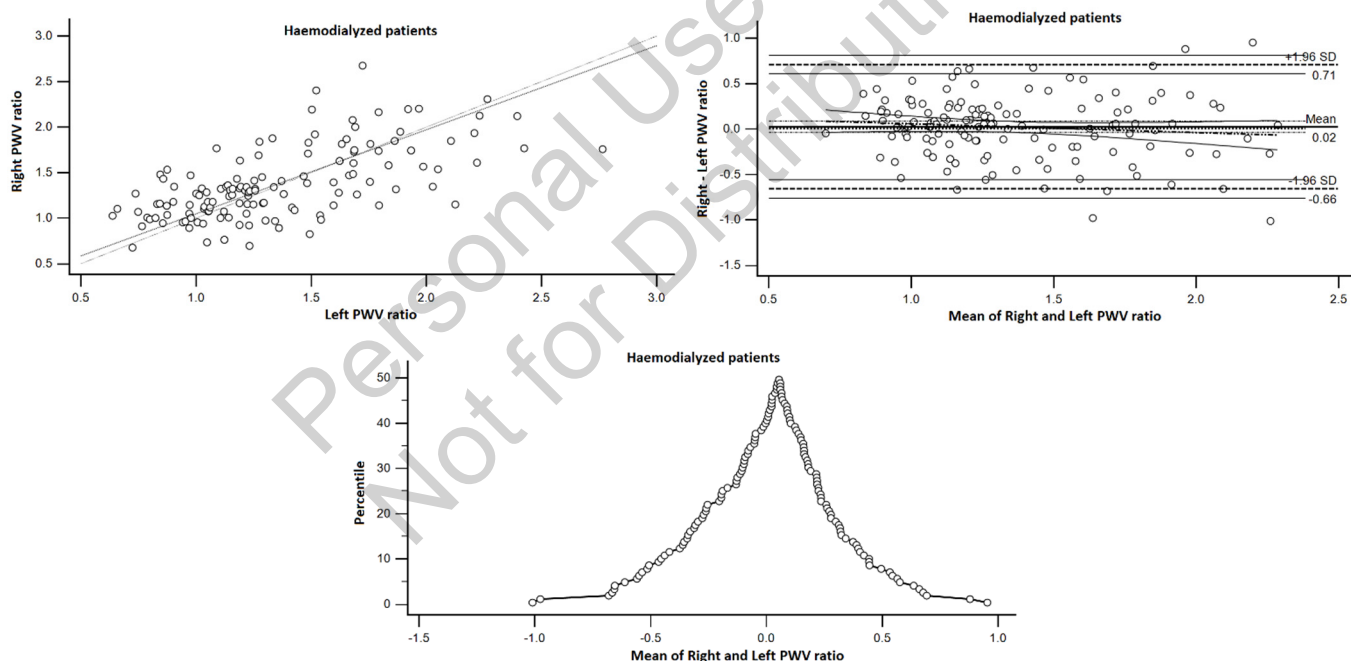


Fig. (3). Left upper panel: pulse wave velocity (PWV) ratio calculated using arterial stiffness data obtained in the left side of the body, are correlated with the right PWV-ratio (n=135). Upper right and bottom panels: Bland & Altman analysis and Mountain plot allow to visualize data used in the correlation study.

with high correlation values. Additionally, these figures of Bland & Altman and Mountain plots allow to visualize the information provided in Table 3.

4. DISCUSSION

The stiffness gradient between aortic and peripheral arteries calculated as cf-PWV/cr-PWV ratio was reported to be significantly associated with increased mortality in hemodia-

lyzed patients [5, 14]. In another cohort of hemodialyzed patients, London *et al.* [6] reported, in 2016, an index destined to evaluate central and peripheral stiffness using a formula $[(\text{brachial PWV}/\text{aortic PWV})^{0.5}]$ different from that used by Fortier *et al.* [5]. The research by London *et al.* found that this stiffness gradient was associated to all-cause and cardiovascular mortality, but they attributed the predictive value of this index only due to the aortic stiffness

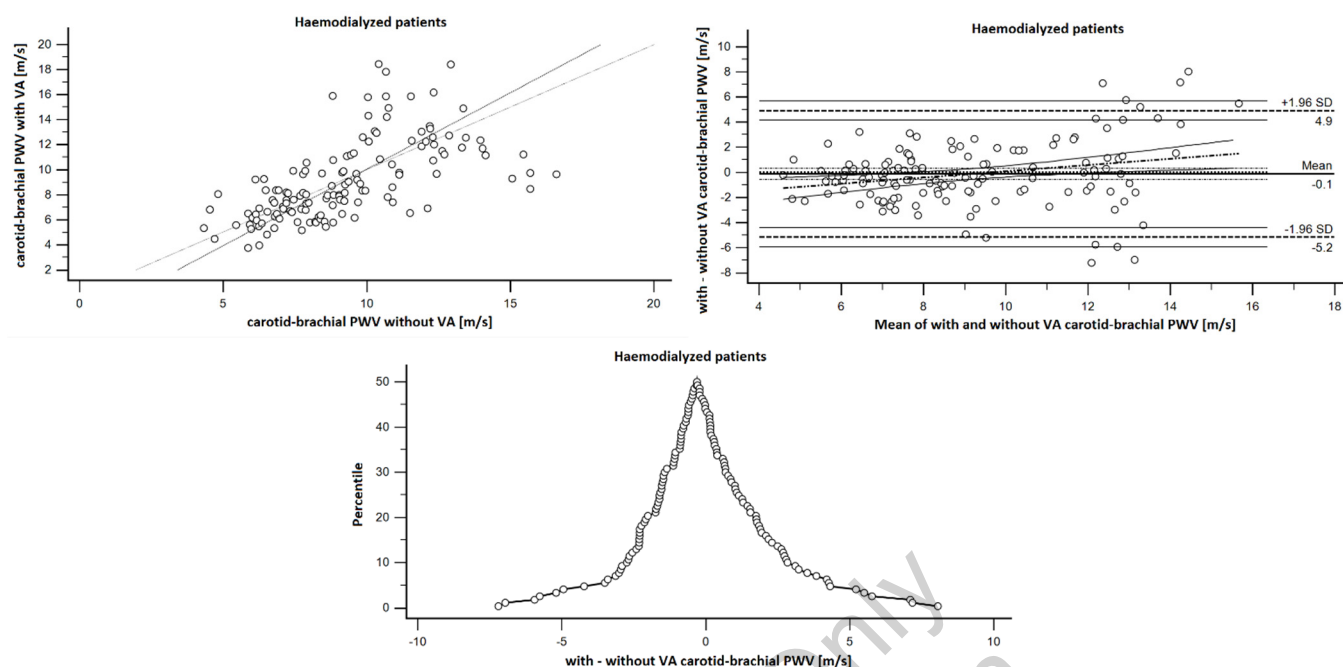


Fig. (4). Upper left panel: carotid-brachial pulse wave velocity (PWV) obtained in the upper-limb with the vascular access (VA) is correlated with PWV measured in the contralateral intact upper limb arterial pathway (n=135). Upper right and bottom panels: Bland & Altman analysis and Mountain plot allow to visualize data used in the correlation study.

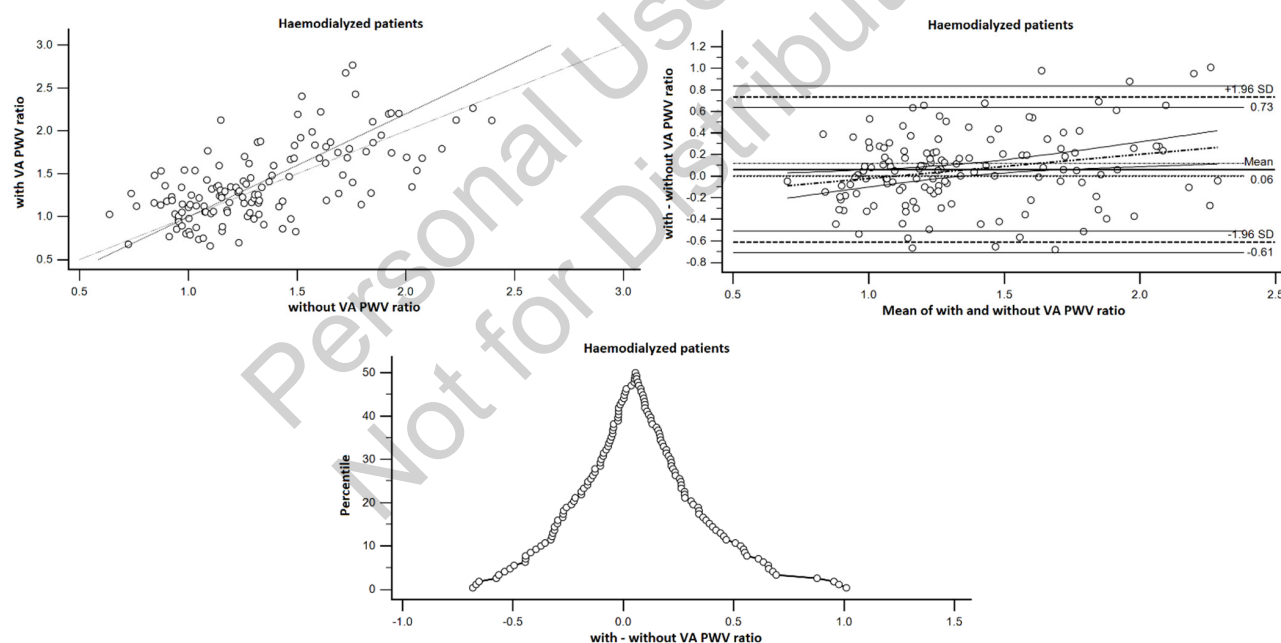


Fig. (5). Upper left panel: pulse wave velocity (PWV) ratio calculated with stiffness data obtained in the left side of the body with the vascular access (VA) is correlated with PWV calculated in the contralateral side of the body (n=135). Upper right and bottom panels: Bland & Altman analysis and Mountain plot allow to visualize data used in the correlation study.

changes [6]. Then, the PWV-ratio index developed by Fortier *et al.* was strongly associated with the extent of aortic arch calcification in hemodialyzed patients [7]. However, when this arterial gradient [15] was used in a non-dialyzed community, no prognostic value could be proved in a cohort of 2114 Framingham Heart study subjects [16]. Our group recently reported a 5-year follow-up study of hemodialyzed patients in whom PWV-ratio was calculated [8]. PWV-ratio

evaluated after 5 years of hemodialysis showed a significant increase with respect to their initial values; however, these patients also exhibit a reduction of both cf-PWV and cr-PWV values ($p < 0.001$). This result, obtained in ESRD patients, may seem paradoxical, since the proposed indexes show an impairment in terms of arterial stiffness, while an improvement (*i.e.* a decrease) was shown in terms of cf-PWV and the cr-PWV values [8].

Table 3. Bland & Altman analysis information: carotid-femoral and carotid-brachial PWV and PWV ratio in hemodialyzed patients.

	Right (Reference) vs. Left Hemi Body			Upper Limb With (Reference) vs. Without VA	
	Carotid-femoral PWV	Carotid-brachial PWV	PWV Ratio	Carotid-brachial PWV	PWV Ratio
Mean error	0.3032	-0.272	0.0223	-0.1294	0.05977
95% C.I.	0.01951 / 0.5868	-0.7032 / 0.1593	-0.03725 / 0.08185	-0.5673 / 0.3085	0.0012 / 0.1182
P*	0.0366	0.2144	0.4601	0.05599	0.0452
SD	1.0981	2.5141	0.3485	2.5727	0.3435
Lower Limit	-1.8491	-5.1995	-0.6608	-5.1718	-0.6135
95%C.I.	-2.3365 / -1.3616	-5.9383 / -4.4607	-0.7628 / -0.5587	-5.9221 to -4.4215	-0.7137 / -0.5134
Upper limit	2.4554	4.6556	0.7054	4.913	0.7331
95% C.I.	1.9679 / 2.9429	3.9168 / 5.3944	0.6034 / 0.8074	4.1627 / 5.6633	0.6329 / 0.8333
Equation	$y=0.5068 - 0.02066x$	$y=0.8987 - 0.1288x$	$y=0.1550 - 0.09744x$	$y=-2.411+0.248x$	$y=-0.244+0.223x$
Intercept					
Coefficient	0.5068	0.8987	0.155	-2.4115	-0.244
SE	0.5171	0.818	0.116	0.794	0.111
t-value	0.9801	1.0986	1.3362	-3.0371	-2.1973
P	0.3311	0.274	0.1838	0.0029	0.0297
95% C.I.	-0.5283 / 1.5420	-0.7196 / 2.5169	-0.07444 / 0.3844	-3.9821 / -0.8410	-0.4636 / -0.02436
Slope					
Coefficient	-0.02066	-0.1288	-0.09744	0.2487	0.2235
SE	0.05042	0.08678	0.08227	0.0833	0.07891
t-value	-0.4097	-1.4842	-1.1844	2.9858	2.8326
p value	0.6835	0.1401	0.2384	0.0034	0.0053
95% CI	-0.1216 to 0.08026	-0.3005 to 0.04287	-0.2602 to 0.06530	0.08395 / 0.4135	0.06744 / 0.3796

PWV: pulse wave velocity. C.I.: confidence interval. SE and SD: standard error and deviation. $p < 0.05$ was considered significant. *(H0: Mean=0).

Both hemodialyzed and non-hemodialyzed patients included in this study showed high correlation coefficients when the right and left sides of the body were analyzed in terms of cf-PWV, cb-PWV and PWV-ratio (Figs. 1-5). In the non-hemodialyzed cohort, no differences were found when right and left cf-PWV, cb-PWV and PWV-ratio were compared. On the other hand, in the hemodialyzed cohort, these parameters were clearly different when the side of the body side in which the vascular access was placed was compared to its contralateral intact side.

Independently of the usefulness of the PWV-ratio, we showed that the calculated value of this new index depends on the observed side of the body, and that the vascular access localization is the determinant factor of the differences in terms of arterial stiffness.

One limitation of the present research is the measurement of cb-PWV that we chose to evaluate the brachial arteries, instead of cr-PWV pathway. The latter has been widely used

in the past and in the last years in order to calculate PWV-ratio [5, 7, 16]. This is clearly a limitation when comparing our findings to others previously reported. However, since vascular access construction currently uses the radial artery in the arteriovenous anastomosis, we chose to analyze the carotid-brachial pathway free of any surgical intervention, in order to minimize geometrical modifications. In the analysis of arterial stiffness, the integrity of the vascular structure is very important, since PWV values integrates arterial geometry and intrinsic elastic properties [17].

Finally, according to our results, the anatomical differences in normal subjects and the above-mentioned geometrical and structural changes in pathological states, we consider that more studies are necessary to elucidate the real influence of the arterial region in which the vascular stiffness is analyzed. A correct interpretation of arterial stiffness data could allow to improve the usefulness of the increased indication of this non-invasive evaluation of arteries in hemodialyzed patients [18].

CONCLUSION

In the hemodialyzed patients included in this research, PWV-ratio values obtained on the side of the body were the arteriovenous fistulae which were placed significantly higher than those obtained in the contralateral side. Moreover, cf-PWV, cb-PWV and PWV-ratio values obtained on one body side, were always significantly correlated with the contralateral side. According to our research, any research involving calculi of PWV-ratio should be considered which territory is analyzed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by our Institutional Review Board and Ethics Committee.

HUMAN AND ANIMAL RIGHTS

All clinical investigations have been conducted according to the declaration of Helsinki principles.

CONSENT FOR PUBLICATION

All patients gave their written consent.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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