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REVIEW ARTICLE

Arterial Stiffness in Haemodialyzed Patients: Findings and Controversies

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Abstract: Vascular research in end-stage renal diseases is an interesting field in which the characterization of arterial stiffness proved to be valuable to predict morbidity and mortality. Particularly, patients on renal replacement therapy have been reported to have significant increases in arterial stiffness and cardiovascular mortality. The clinical relevance of the measurement of arterial stiffness is linked to therapeutical and preventive interventions. The purpose of this work is to analyze the results of the scientific research in the field of arterial stiffness, in which hemodialyzed patients were involved, emphasizing on clinical and *in-vitro* research carried out by our group compared to contributions previously reported in the specialized literature. These investigations are necessary to improve diagnostic strategies and monitor the arterial response to therapeutical interventions in chronic kidney disease.

Keywords: Arterial stiffness, aortic stiffness, pulse wave velocity, hemodialysis, vascular access, chronic kidney disease.

1. INTRODUCTION

Vascular research in End-Stage Renal Diseases (ESRD) is an interesting field in which the characterization of arterial stiffness proved to be valuable to predict morbidity and mortality. Arterial stiffness, which describes the resistance of arterial wall to deformation, is a physical property that is currently assessed in humans using invasive and non-invasive indices, such as the elastic modulus, arterial distensibility, volume compliance, Young's modulus, pulse wave velocity (PWV), and stiffness index. In physiological states, the values of arterial stiffness increase from the aortic root towards peripheral territories

Arterial stiffness evaluated in the aortic pathway has shown to have relevance as a predictor of morbidity and mortality, since it is a marker of increased cardiovascular risk, including stroke, cardiac failure and myocardial infarction. In the general population, the stiffening process of arteries occurs physiologically with aging but shows a high correlation with the prevalence of atherosclerosis.

The pathogenesis of arterial stiffening is a complex process that involves the alteration of elastin and collagen in the vascular wall, and endothelial and smooth muscle dysfunction accompanied by inflammation and oxidation stress, among other factors. Aortic stiffening is a process with a structural base, in which the main components of the vascular wall are involved. Elastic lamellae show fractures and disorganization accompanied by increases in collagen content of the arterial wall. Age-related factors, diseases and risk factors are involved in the above-mentioned changes, with consequent increases of arterial stiffness. This stiffening process is also observed during arterial calcification and deposition of advanced glycation end-products. Illness-related factors such as chronic kidney disease, diabetes, hypertension, smoking, calcium and phosphate imbalances, increase aortic stiffness well beyond the physiological aging process. Particularly, patients on renal replacement therapy have been reported to have significant increases in arterial stiffness and cardiovascular mortality [1, 2].

The purpose of this review is to analyze results of scientific research in the field of arterial stiffness where hemodialyzed patients were involved, emphasizing on clinical and *in vitro* studies carried out by our group compared with previously reported contributions in the specialized literature.

2. AORTIC STIFFNESS IN HEMODIALYZED PATIENTS

Arterial stiffening is a well-recognized process that occurs during ESRD; the improvement of dialysis technologies determined significant survival increases during the last decades, which allowed to visualize the evolution of arterial stiffness undergoing dialysis throughout the years. Moreover, since these patients see an improvement of life in quan-

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titative and qualitative terms, they may eventually suffer age-related diseases.

A pioneer investigation by Blacher *et al*. showed that the incremental elastic modulus (Einc: the higher the Einc, the higher the vascular stiffness) assessed in carotid arteries of hemodialyzed patients was an important independent predictor of all-cause and cardiovascular mortality [1]. This result was also confirmed when, in a similar cohort, arterial stiffness was evaluated by measuring carotid-femoral PWV (cfPWV) [2].

In later years, Wang *et al*. showed that chronic kidney disease was accompanied by a stepwise increase in arterial stiffness concomitantly with stages 1-5 [3]. The authors were aware of the high prevalence of cardiovascular risk factors and cardiovascular disease in the analyzed cohort. Furthermore, increases in arterial stiffness were demonstrated in hemodialyzed pediatric patients, in which renal replacement therapy was unable to improve the abnormal arterial wall elastic properties [4].

Previously, in longitudinal investigations, Guerin and London had demonstrated changes in aortic stiffness in a follow-up study that included hemodialyzed patients [5, 6]. These authors reported that, along a 5-year follow-up, a group of patients improved their blood pressure and cfPWV values. Consequently, they divided the observed cohort of hemodialyzed patients into *responders* and *non-responders*. Decreases of left ventricular hypertrophy, blood pressure and aortic stiffness were demonstrated in the *responders* group, while *non-responders* showed no changes or increases in terms of cfPWV values.

In 2015, our group reported a 5-year follow-up study, between 2007 and 2012, in 25 hemodialyzed patients. The analyzed cohort showed a significant decrease in aortic stiffness, evaluated through cfPWV measurements [7]. This significant improvement of arterial stiffness was attributed to arterial pressure management, arteriovenous fistula construction and appropriate renal replacement therapy.

In the specialized literature, there are many reports whose main findings are increases in aortic stiffness in patients on renal replacement therapy [8]. This high-risk population also suffers arterial stiffening due to aging. On the other hand, and according to the analyzed literature [8], the multifactorial origins of aortic stiffening include: tissue calcinosis, hydration status (overload), abnormal blood pressure (hypertension), C-reactive protein serum levels, endothelial dysfunction, Phosphate plasmatic levels, salt intake, Advanced Glycation End products (AGEs) and plasmatic albumin levels.

Among the observed chronic kidney disease and aortic stiffness studies, the one by Kheder-Elfekih *et al*. best represents all of them. The state of arteries is evaluated through traditional risk factors, new risk biomarkers, therapeutic interventions, microvascular damage and biophysics variables [9]. The authors concluded that with the absence of an appropriate renal replacement therapy or kidney transplantation, arterial stiffening is a major cardiovascular risk in subjects with chronic kidney disease.

Considering the poor prognosis for patients with ESRD, our group analyzed a cohort of hemodialyzed patients in terms of their early vascular aging (EVA) characterized by the slope of the cfPWV-Age and βPWC-age relationships [10]. We found a significant EVA reduction along a five-year follow-up. Interestingly, no association was found between arterial blood pressure levels and the above-mentioned arterial stiffness indices. Moreover, an etiological analysis of the pathologies responsible for the ESRD was performed, showing that diabetic nephropathy and nephroangiosclerosis had the higher levels of arterial stiffness [10]. This is an important finding, since the observed cohort showed an accelerated aortic stiffening process in terms of EVA, with diabetic nephropathy patients showing the higher EVA increase. According to our results, hemodialysis patients are not only a high-risk group, but also an inhomogeneous population.

3. UPPER-LIMB ARTERIAL STIFFNESS IN HEMODIALYZED PATIENTS

ESRD patients usually show a vascular stiffening process that is particularly evident in the aortic pathway. Interestingly, it has been reported that the construction of an arteriovenous fistula reduces arterial blood pressure [11-13]. Moreover, arteriovenous fistula construction has been involved in a process of cfPWV reduction [11]. However, not all systemic arteries are uniformly affected; indeed, upper-limb arterial elasticity changes have been previously reported [11].

Several authors have pointed out that hemodialyzed patients show decreases of arterial stiffness in upper-limb arteries, which seems counterintuitive. This paradoxical finding was also reported in hemodialyzed cohorts that included hypertensive patients. In 2009, our group showed, in a cohort of hemodialyzed patients, that carotid-brachial PWV (cbPWV) was reduced in the upper-limb in which the arteriovenous fistula was placed with respect to its contralateral (*i.e*. untouched) pathway [14]. Utescu *et al*. also found, in a similar cohort, non-significant decreases in carotid-radial PWV (crPWV), comparing pre- and post- arteriovenous fistula construction values (9.3 ± 2.2 versus 8.9 ± 1.6 m/s; p=0.16) [15].

Later, in 2012, our group reported that vascular access for haemodialysis constructed in the upper-arm determined a greater reduction in cbPWV than those in the forearm [16]. Simultaneously, Utescu *et al*. demonstrated that crPWV measured in the intact upper-limb was significantly reduced in ESRD patients, comparing values obtained before and after constructing the arteriovenous fistula [17].

The observed decreases in cbPWV in hemodialyzed patients analyzed by our group could be attributed to the remodeling process determined by the high shear-stress produced by the vascular access confection. Furthermore, geometrical factors involving the increase of arterial diameter may explain the decrease of cbPWV found in the upper-limb with the arteriovenous shunt with respect to its contralateral intact vascular pathway [14].

The above-mentioned works showed decreases in upper-limb PWV in hemodialyzed patients that were accompanied by abnormal increases in aortic stiffness. This finding was analyzed by several authors. Fortier *et al*. hypothesized that, in ESRD patients, increases in aortic stiffness accompanied

by peripheral arterial stiffness decreases could be due to a compensatory mechanism. In fact, arterial stiffness measured in the aortic pathway is normally lower than in muscular arteries and, hypothetically, an increase in central arterial stiffness could be the cause of a compensatory decrease of peripheral artery stiffness [4]. This important issue determined the need to develop new indices of arterial function, commented in the following section.

4. ARTERIAL STIFFNESS AND VASCULAR ACCESSES

Renal replacement therapy achieves prolonged survival for end-stage renal disease patients. Furthermore, an improvement in the quality of life is currently observed in clinical practice. Hemodialysis is usually performed three times per week, by connecting the patient to an extracorporeal blood circulating loop. Currently, the vascular access that allows this procedure is the arteriovenous shunt, made with native vessels or using a synthetic prosthesis [18, 19]. A continuous arteriovenous shunt brings hemodynamic changes, such as increase of cardiac output and heart rate, accompanied by decreases in peripheral systemic resistances. These changes determine an imbalance between subendocardial oxygen supply and an increase of oxygen demand, determined by the increase in myocardial consumption [20, 21]. Moreover, vascular accesses have a high incidence of complications, such as infections, vascular steal syndrome, thrombotic occlusion, luminal stenosis and intimal hyperplasia [22].

As previously mentioned, the arteriovenous shunt is done using native vessels that are usually the radial artery and cephalic vein in the forearm [19]. This procedure has shown to provide the longest patency rate in hemodialyzed patients [19]. However, some patients do not have adequate vessels to use as arteriovenous shunts, or all vessels have been used in previous vascular accesses. In these cases, a prosthetic material is interposed between the native artery and a vein; currently, expanded polytetrafluoroethylene grafts are used [20].

Regardless the nature of vascular access, blood flow increases are accompanied by the development of intimal hyperplasia. This entity is characterized by the denudation of endothelial cells and the cumulus of platelets and leucocytes on the vessel wall [23, 24]. The mechanism involved in intimal hyperplasia development has not been entirely clarified [25]. Several authors point out that intimal hyperplasia is the consequence of high flow rates in vessels used to make the vascular access [24]. During this anomalous process, the disturbed blood flow causes cellular and extracellular matrix proliferation in the intima layer, forcing endovascular interventions in a large population of hemodialyzed patients [26].

The development of intimal hyperplasia has also been linked to the increased wall shear-stress and the elastic mismatch between the native vessels and the grafts (either synthetic or native) used for the vascular access [27]. Our group studied the complex nature of hemodynamic changes determined by the vascular access by means of the mechanical properties of human vessels currently used in arteriovenous fistula confection. With this purpose, an *in-vitro* analysis was carried out, using vascular segments submitted to diverse ranges of intraluminal pressure and stretching rate values [28-30].

The circulation loop used in this research is made up of a pneumatic pump (Jarvik model 7, Kolff Medical, Salt Lake City, UT) that propels the fluid through the circuit. A pulsatile flow is circulated through a perfusion line that takes the fluid from a reservoir with Tyrode's solution kept at 37ºC with a pH of 7.4 bubbled with 100% oxygen. Changes in fluid dynamics were achieved through a resistance modulator, using a console to mimic the human circulatory system adaptation (Jarvik 7 driver). See Fig. (**1**). Pressure and diameter vascular signals were obtained using a Konigsberg P7 or P2.5 micro transducer (1200 Hz frequency response) and a pair of ultrasonic crystals (5 MHz, 2 mm diameter); respectively. This hydraulic simulator has been previously used by our group [30].

Data were analyzed to calculate arterial elasticity and viscosity using previously reported methods [31, 32], which uses the pressure-diameter relationship (see Fig. **2**). As seen in Table **1**, our results showed that both the elastic index and viscous values of native jugular veins were significantly different from brachial and femoral arteries harvested from human cadaveric donors.

These findings suggest that an arteriovenous shunt done with native vessels have significant elastic and viscous mismatches [33]. The elastic mismatch has been considered one of the factors involved in the development of intimal hyperplasia found in vessels used to construct arteriovenous shunts in hemodialyzed patients [27].

Additionally, we reported that the ePTFE showed a negligible viscosity [35-37] accompanied by extremely high elastic values [31]. This synthetic prosthesis, mostly used in arteriovenous shunts, has very different viscoelastic properties than those observed in native vessels.

Our results characterized the dynamic characteristics of biologic and synthetic vessels used in arteriovenous shunt confection from a mechanical point of view [33], which have

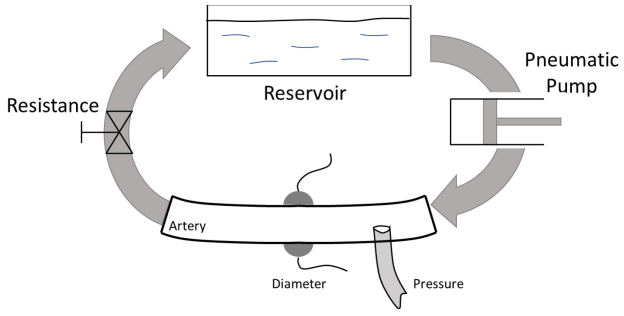

Fig. (1). Circulation Loop. A pneumatic pump generates cyclic pressure-diameter changes in an arterial segment. The flow rate and resistances are modulated during each experimental session. A reservoir allows performing changes in the circulating fluid: hematocrit, drug infusion, among others. The intraluminal pressure signal is obtained with a solid pressure micro transducer and vascular diameter using ultrasonic crystals. Arrows indicate flow direction.

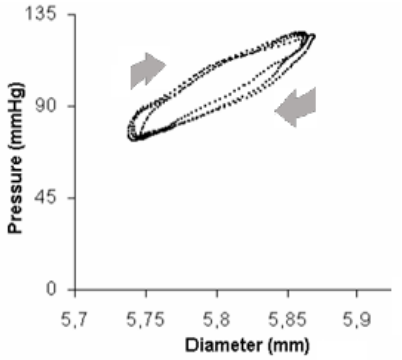

Fig. (2). *In vitro* pressure-diameter signals obtained in an ovine femoral artery. Both signals are plotted against each other, yielding a clockwise pressure-diameter loop. Reproduced from Bia *et al*. with permission [34].

Table 1. Biomechanical parameters of human vessels (n = 7).

	E	η
Saphenous vein	$958.45 \pm 75.31^{A,B}$	$4.17 \pm 0.52^{A,B}$
Brachial artery	417.23 ± 36.21	12.01 ± 1.44
Femoral artery	628.27 ± 164.23	18.63 ± 3.43

Values are mean ± SD. E: elastic index (mmHg/mm). η: viscous index (mmHg.s/mm). p values were determined by one-way analysis of variance followed by Bonferroni test. A: $p<0.05$ with respect to Brachial artery values; B: $p<0.05$ with respect to Femoral artery values. Data previously reported, reproduced with permission [33].

local and systemic consequences in the cardiovascular system [37].

5. HYDRATION STATUS AND ARTERIAL STIFFNESS IN HEMODIALYZED PATIENTS

Hemodialyzed patients have risk factors, such as malnutrition, derived from their hydration status. Currently, overload is considered a predictor of outcome in ESRD [38, 39]. Volume overhydration is accompanied by systemic arterial hypertension; however, this increase in blood pressure is not always fluid-dependent in hemodialyzed patients [40]. Currently, new techniques allow to accurately assess hydration status, allowing to analyze the real value of fluid changes evaluated in different body compartments. Hur *et al*. showed that hydration status evaluated through bioimpedance spectroscopy is a useful tool in medical practice that allows an improvement in the management of body fluid in hemodialyzed patients [41].

Our group analyzed the hydration status of hemodialyzed patients and the vascular stiffness evaluated in muscular and arterial arteries. Hydration status was evaluated by analyzing extracellular/intracellular fluid, extracellular/Total Body Fluid, relative overhydration and absolute overhydration [42]. In the analyzed cohort, we demonstrated that aortic stiffness evaluated through cfPWV was positively associated with the hydration status of the patient. On the other hand, crPWV was not associated with the hydration status of patients.

The association between hydration status and PWV ratio was also analyzed by our group in hemodialyzed patients. This research had been previously proposed by Fortier *et al*. in the discussion section of their work [18]. In our research, we focused our attention on the factors involved in the arterial stiffening process, including the etiologies of ESRD. In the analyzed cohort, we found that patients in hemodialysis have higher values of PWV ratio with respect to those belonging to the healthy control group [43]. The higher the PWV ratio, the higher the risk of mortality [18]. Interestingly, in our cohort, the PWV ratio increase was not uniform, and we demonstrated that diabetic nephropathy had the highest arterial stiffness mismatch evaluated through this new index, with respect to non-diabetic patients [43].

6. STIFFNESS INDICES USED IN HEMODIALYZED PATIENTS

Arterial stiffness has been assessed through PWV for a long time, and several methods of elastic arterial characterization were used to evaluate specific territories and to compare different vascular pathways. First, PWV was assessed in the carotid-radial pathway [44]. Then, aortic stiffness evaluated through cfPWV proved to be a prognostic biomarker identifying hemodialyzed patients at risk of cardiovascular disease [2]. This conclusion was confirmed by several authors, and PWV measurements turned towards the carotid-femoral pathway, without considering the evaluation of the carotid radial territory.

Twenty years later, the demonstration of significant changes in arterial stiffness measured in the carotid radial pathway through PWV, led to this territory being included in clinical research in hemodialyzed patients [14]. The work by Utescu *et al*. showed a non-significant decrease of crPWV in 31 hemodialyzed patients, comparing values obtained before and 3 months after constructing an arteriovenous fistula (from 9.3 ± 2.2 to 8.9 ± 1.6 m/s; $p = 0.16$). Interestingly, the same group reported, in 2013, a second research in 109 hemodialyzed patients, in which measurements of crPWV were evaluated 1.2 years after placing the vascular access [17]. In this follow-up, the authors demonstrated a significant decrease of crPWV when comparing pre- and post-arteriovenous fistula implantation values (from 8.80±1.86 to 8.05±1.67 m/s; $p<0.001$).

As mentioned above, our group showed in 2009 that PWV measured in the carotid-brachial pathway where the vascular access for hemodialysis was placed was significantly lower than that obtained in its contralateral intact upper-limb [14]. Moreover, these differences were significantly higher when the arteriovenous shunt was made in the brachial artery, compared to those of made in the forearm [16].

Utescu *et al*. demonstrated significant decreases of upper-limb arterial stiffness in hemodialyzed patients comparing crPWV values obtained in intact arteries before and after the confection of the vascular access. On the other hand, our group demonstrated that PWV measured in the upper-limb where the arteriovenous fistula was placed was significantly lower than that obtained in its contralateral intact carotid-brachial pathway. Thus, Utescu and coworkers showed the evolution of crPWV [15] and our group characterized the

functional local consequences of the vascular access for hemodialysis [14].

In 2015, a biomechanical mismatch between cfPWV and crPWV was used to characterize aortic-peripheral stiffness changes in hemodialyzed patients. Fortier *et al*. calculated PWV ratio as [18]:

PWV ratio = cfPWV/crPWV

London *et al*. reported an index to evaluate the stiffness gradient between central and peripheral arterial territories [45, 46]. The authors calculated this gradient as: (brachialPWV/aorticPWV) · 0.5. Central and peripheral territories have a different position, but London *et al*. considered that both may be used to measure the stiffness gradient.

PWV ratio, calculated according to the formula reported by Fortier *et al*. was significantly associated with increased mortality in a cohort of hemodialyzed patients [18].

Our group published a Letter to the Editor [47] regarding the index used by Fortier *et al*., where some limitations of the method were considered linked to the assumption that aortic stiffness in dialyzed patients increases, while simultaneously decreasing in the carotid-radial pathway. However, this is not a general rule, as previously reported by several authors [6]. Moreover, as PWV ratio is used in hemodialyzed patients, it is important to consider our previous works, in which differences between left and right upper-limb PWV showed statistically different values [14]. Furthermore, these differences were significantly higher when the arteriovenous shunt was placed in the brachial artery, compared to those of the forearm [16]. According to our results, the calculated value of PWV ratio or gradient could be different depending on the nature of the analyzed vascular territory. Another issue to consider is that hemodialyzed patients currently exhibit at least one functioning vascular access accompanied by surgically modified vessels in the contralateral upper limb (*i.e*. a previous shunt). Summarizing, the use of PWV ratio or PWV gradient [48, 49] should be restricted to hemodialyzed patients with one remaining intact upper-limb arterial territory.

Another limitation of PWV ratio is its use in a non-dialyzed community, due to its inability to provide prognostic value in a cohort of 2114 Framingham Heart study subjects [50].

Our group has recently reported a 5-year follow-up of hemodialyzed patients in which PWV ratio was calculated [43]. We showed that 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 cfPWV and crPWV ($p<0.001$). This result, obtained in ESRD patients, could be at least considered paradoxical, since the proposed index shows an impairment in terms of arterial stiffness, while an improvement (*i.e.* a decrease) is demonstrated with the well-known cfPWV and the crPWV.

7. FINAL COMMENTS

As mentioned above, chronic kidney disease is a process accompanied by a stepwise increase in aortic stiffness concomitant with stages 1-5 [3]. The hemodialyzed population includes patients that improve in terms of arterial stiffness, left ventricular hypertrophy and blood pressure [5, 6]. This observed improvement is in line with a previous work reported by our group [7]. However, decreases in aortic stiffness in hemodialyzed patients are not always observed, and several factors could be involved, such as hydration status, arterial pressure management, arteriovenous fistula construction and appropriate renal replacement therapy. Evidently, factors beyond renal replacement therapy are involved in the clinical condition of chronic kidney disease patients.

Brachial artery stiffness, measured in the upper-limb where the vascular access is constructed, is a determinant of the elastic mismatch found between vessels used to make arteriovenous shunts in hemodialyzed patients. This elastic mismatch is a factor involved in the development of intimal hyperplasia in vessels used to construct arteriovenous shunts [27, 28, 36]. On the other hand, measurements of arterial stiffness have been used to calculate the PWV ratio, a new index with clinical connotations. According to Fortier *et al*., this index was significantly associated with increased mortality in a cohort of hemodialyzed patients [18]. Limitations in the use of this index should be clarified in future investigations carried out with hemodialyzed and non-hemodialyzed patients.

The clinical relevance of the measurement of arterial stiffness is linked to therapeutical and preventive interventions, done to improve the prognosis of patients in renal replacement therapy. As previously mentioned, several authors have demonstrated improvements and impairments in terms of arterial stiffness. The differentiated evolution of these patients are linked to well-known cardiovascular risk factor management and decreases in arterial stiffness [3, 5, 6, 18].

CONCLUSION

Finally, the analyzed literature shows the relevance of the assessment of arterial stiffness in hemodialyzed patients. Indeed, cfPWV and crPWV provide information about the real state of both elastic and muscular arteries, respectively. Since new technologies are currently being developed to investigate the nature of the arterial disease, more research is needed to improve diagnostic strategies and monitoring the arterial response to therapeutical interventions in chronic kidney disease patients.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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

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