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Variation of hemodialysis related arterial stiffness in patients with end stage renal disease

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Abstract. Objective: Cardiovascular disease is the leading cause of morbidity and mortality in patients undergoing hemodialysis. Increased arterial stiffness is an independent predictor of cardiovascular mortality in end stage renal disease (ESRD). We hypothesized that the hemodialysis procedure itself, through alterations in electrolytes and blood volume, could contribute to the increased cardiovascular risk encountered in ESRD. Material and methods: 28 chronic hemodialysis patients were evaluated before and after hemodialysis. We determined serum calcium, arterial stiffness (using pulse wave analysis) and hemodynamic parameters. Results: Serum calcium increased significantly during the dialysis treatment ($P<0.01$). Also, significant increase in stiffness index occurred at the end of dialysis ($P=0.02$). Both increments were correlated with ultrafiltration. No significant changes in systolic blood pressure, diastolic blood pressure or heart rate were noticed during hemodialysis. Arterial stiffness significantly increased after hemodialysis, unrelated to hemodynamic parameters. Conclusion: This vascular response may be an explanation for greater vulnerability regarding cardiovascular events in ESRD patients.
Key Words: hemodialysis, cardiovascular risk, arterial stiffness, ultrafiltration, calcium.

Rezumat. Obiectiv**:** Boala cardiovasculară constituie principala cauză de morbiditate şi mortalitate la pacienţii dializaţi. Creşterea rigidităţii arteriale este un factor predictiv independent pentru mortalitatea cardiovasculară la pacienţii cu boala cronică renală aflată în stadiul terminal. Am emis ipoteza că, însăşi procedura de dializă, prin modificările pe care le produce, la nivel de electroliţi şi volum sangvin, poate contribui la creşterea riscului cardiovascular la aceşti pacienţi. Material şi metodă : Au fost evaluaţi 28 de pacienţi pre- si postdializă. S-a determinat calciul seric, indicele de rigiditate (utilizând analiza undei de puls) şi parametri hemodinamici. Rezultate: Nivelul calciului seric a crescut semnificativ în timpul dializei ($P<0.01$). De asemeni, la sfârşitul dializei apare o creştere semnificativă a indicelui de rigiditate ($P=0.02$). Amândouă creşterile au corelat cu ultrafiltrarea. Nu au fost înregistrate creşteri semnificative ale tensiunii arteriale sistolice, diastolice sau ale ratei pulsului. Rigiditatea arterială a crescut semnificativ după dializă, fără legătură cu parametri hemodianamici. Concluzie: Acest răspuns vascular poate constitui o explicaţie a vulnerabilităţii crescute la evenimente cardiovasculare a acestor pacienţi.
Cuvinte cheie: hemodializa, risc cardiovascular, rigiditate arterială, ultrafiltrare, calciu.

Introduction. Cardiovascular disease is the main cause of morbidity and mortality among patients with ESRD undergoing hemodialysis, according to the literature (Foley 1998).

Alterations of the vascular mechanical properties and endothelial dysfunction are frequent in chronic renal failure, leading to an increase in cardiovascular morbidity and mortality, as it was shown (Blacher et al 1999). An increase in arterial stiffness reduces the compliance of the large arteries, with a subsequent increase in the ventricular afterload, followed by left ventricular hypertrophy and reduced coronary perfusion (London 2002). Recently, arterial stiffness has been described by many authors (Laurent 2002; Pannier 2005; Agarwal 2007) as an independent predictive factor for cardiovascular mortality and survival in patients on hemodialysis.

Although the mechanisms responsible for increased arterial stiffness in patients with ESRD are not yet fully understood, there are general and specific factors described in this population (Guerin et al 2008). The main factors involved in arterial stiffness progression in patients on hemodialysis are shown in Table 1.

Table 1

Determinant factors of arterial stiffness

General factors	*Specific factors*
Age	Sodium balance
Diabetes mellitus	Renin-angiotensin-aldosterone system
Arterial hypertension	Anaemia
Smoking	Mineral metabolism
Dyslipidemia	Vascular calcification
Metabolic syndrome	Inflammmation
Endothelial dysfunction	Biocompatibilty
	Uremia per se
	Fluid overload
	Ateriovenous fistula

The increase in arterial stiffness can be measured by non-invasive means, using methods that analyze pulse wave morphology, according to some authors (Laurent 2006; De Loach et al 2008; Brillante et al 2008).

The control and treatment of risk factors is important, but the changes in volume, electrolytes and humoral status, caused by hemodialysis procedure itself, contribute to the increasing incidence of cardiovascular disease, as it was shown by Cohen et al 2002.

The purpose of the present study is to estimate the acute effects of hemodialysis on vascular stiffness.

Material and Method. 28 Patients undergoing chronic hemodialysis for at least three months have been included in this study. The main causes of chronic renal failure were: tubulo-interstitial nephropathy (28.75%), nephroangiosclerosis (25%), chronic glomerulonephritis (25%), other chronic nephropathies (14.28%) and polycystic kidney disease (10.71%).

Patients have been evaluated before and after the hemodialysis session. Laboratory biomarkers tested included: lipid profile, total calcium before and after dialysis, parathormone, albumin, and hypersensitive C reactive protein.

Patients underwent hemodialysis with polysulphone, polyamide and hemophane membranes, with each session lasting for at least 4 hours. The effective ultrafiltration was recorded as the difference between the predialysis and postdialysis weight. Also the blood pressure was measured before and after dialysis.

The main characteristics of the patients are presented in Table 2.

Most of the patients had high blood pressure (n=26), and were treated with angiotensin-converting enzyme inhibitors (ACEI), (n=19), a combination of ACEI and calcium channel blockers and/or beta-blockers (n=18).

Arterial stiffness was evaluated by measuring the stiffness index (SI). SI represents a measure of pulse wave velocity in the large arteries. SI was determined with a digital photopletismograph (Pulse Trace PCA2, Micromedical, Rochester, UK). This method is facile and examiner independent. Also, photopletismography has been accepted as having an important epidemiological value. The heart rate (HR) was recorded using the photopletismograph and the systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an adequate sized cuff sphygmomanometer, taking into account the mean value from three consecutive measurements.

Each patient was evaluated in the supine position before and after the dialysis session.

The statistical analysis of the results was performed using the SigmaStat software. Parameters were expressed as mean value ± standard deviation, with a mention of the minimum and maximum value. Correlation was determined using the Pearson test and the t test was used for comparison of the study groups. A P value less than 0.05 was considered statistically significant.

Table 2

The clinical and biochemical characteristics of the patients

Parameter	*Value*
Mean age(years)	53.7 ± 12.5(33-75)
Male/female	13/16
Dialysis duration(months)	64.4 ± 47.6(3-196)
Total cholesterol(mg dl^{-1})	174.9 ± 44.8(83-329)
HDL cholesterol(mg dl^{-1})	38.9 ± 15.5(24-79)
LDL cholesterol(mg dl^{-1})	100 ± 32.6(33-189)
Triglycerides(mg dl^{-1})	171 ± 105(44-411)
Parathormone(pg ml^{-1})	603.1 ± 482.3(95.4-1986)
Total calcium(mg dl^{-1})	8.84 ± 0.89(7.6-10.8)
Calcium-phosphorus product	61.8 ± 21.2(33.4-108)
Albumin(mg dl^{-1})	3.65 ± 0.33(3-4.3)
C reactive protein(mg dl^{-1})	2.18 ± 2.05(0.05-5.67)
Ultrafiltration(L)	2.58 ± 1.22(0-4.7)
Polysulphone membrane	15
Polyamide membrane	4
Hemophane membrane	9

Results and Discussion. There was a statistically significant correlation between SI and male gender (P=0.02) and between SI and duration of dialysis (P=0.04). No statistically significant correlations have been found between SI and other traditional and specific risk factors for arterial stiffness, including the type of membrane used during dialysis.

The difference between SI before and after dialysis was significantly correlated with ultrafiltration (P=0.02), which in turn was correlated with the difference between calcium levels before and after dialysis (P=0.03).

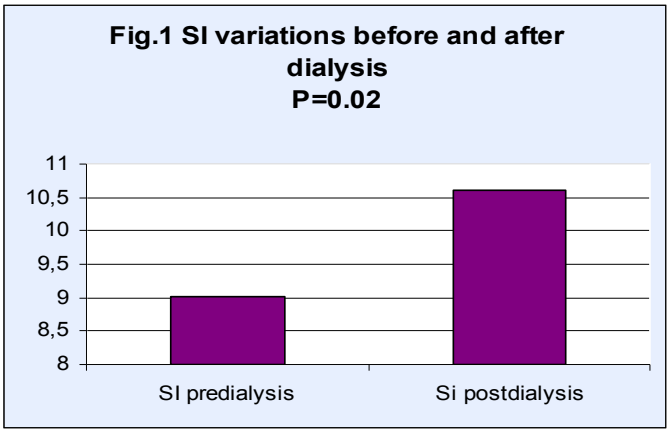
Table 3 presents the parameter values recorded before and after dialysis.

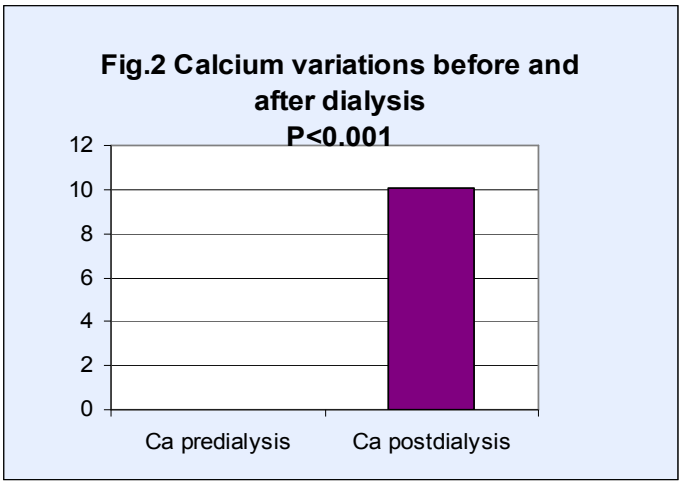
Table 3

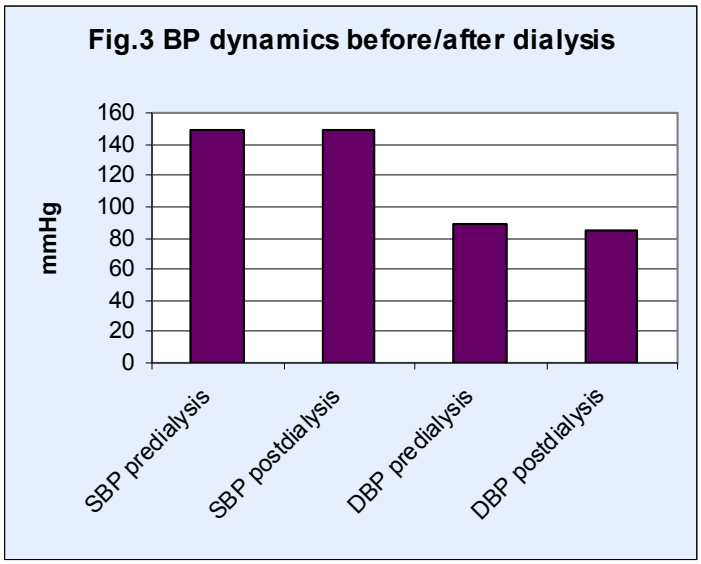
Variations of the functional and biochemical parameters before and after dialysis

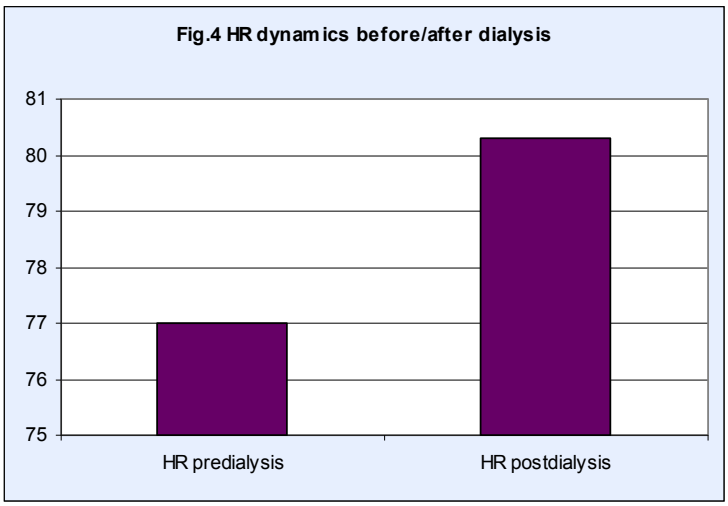
Parameter	*Predialysis*	*Postdialysis*	*P*
SI(m s^{-1})	9.01 ± 2.3(5.7-15.9)	10.6 ± 2.78(4.92-19.5)	**0.02**
SBP(mmHg)	149.7 ± 22.9(110-210)	149.0 ± 2.52(110-220)	0.91
DBP(mmHg)	89.3 ± 14.1(70-130)	85.3 ± 15.2(60-130)	0.26
HR(min^{-1})	77 ± 9.9(60-100)	80.3 ± 9.89(63-100)	0.20
Total calcium(mg dl^{-1})	8.87 ± 0.91(7.6-10.8)	10.1 ± 0.59(9.0-11.2)	**<0.001**

SI was significantly increased after dialysis (P=0.02), as was the total calcium value (P<0.001). There were no statistically significant changes in SBP, DBP and HR before and after dialysis. These variations are shown in Figure 1-4.









The results of the study did not show significant variations of SBP, DBP and HR during a dialysis session. However, there was a significant increase in SI and serum calcium levels, both of them statistically correlated with ultrafiltration.

Fluid volume overload is frequent in hemodialysis patients before dialysis. This state is associated with a higher pulse wave velocity. Due to an increase in arterial distensibility, volume overload increases arterial stiffness. However, ultrafiltration doesn't always reduce arterial stiffness. The results of the studies in this field are contradictory:

- Arterial stiffness can increase after dialysis (Cohen et al 2002; Egresits 2007; Celik 2007; Lin 2005)
- Arterial stiffness increases if the dialysate has a high calcium concentration (Kyriazis et al 2007)
- Arterial stiffness increases with certain types of membranes (Mourad et al 2004)
- Arterial stiffness is constant during dialysis (Kosh 2001)
- Arterial stiffness can be reduced if the patient reaches dry weight and has normal blood pressure at the end of dialysis or if he is treated with ACEI (Covic 2000; Ehy 2005; Mardare 2005; Tycho Vuurmans 2002)

Several explanations have been given for arterial stiffness increase after dialysis 1)blood pressure measurements can be influenced by the fluid imbalance between different body compartments immediately after dialysis or by ''white coat'' effect; 2)electrolyte variations during dialysis - especially calcium, as it was shown by Cohen 2002 and Kyriazis 2007; 3)cardiac status can influence vascular parameters; 4)the neurohumoral response to ultrafiltration - ultrafiltration can induce vascular constriction through the renin-angiotensin system. Elimination of nitric oxide inhibitors through dialysis, associated with an increase in nitric oxide synthesis induced by cytokines released during blood-membrane contact can also alter vascular parameters; 5)dialysis membrane incompatibility revealed by Mourad et al 2004.

The present study showed an increase in arterial stiffness after dialysis, in direct relationship with volume and electrolyte changes. Lack of blood pressure variation could be explained by blood pressure lowering treatment administered during dialysis. None of the patients had significant falls in blood pressure or cramps which would indicate ultrafiltration above dry weight, and the vasoconstriction response was inhibited with medication.

Dry weight is frequently considered empirically, based on clinical criteria (weight of the patient without edema, hypertension or cramps), but nowadays there are complementary paraclinical methods (hematocrit, atrial natriuretic peptide, vena cava diameter, bioimpedance analysis). Using multiple methods to estimate the ideal weight could avoid the consequences of excessive or insufficient ultrafiltration.

Also, individual calcium profile measurement should be performed, in order to maintain a neutral balance. Exposure to a dialysis fluid with a high calcium concentration can lead to hypercalcemia and can aggravate vascular calcification, whilst exposure to low calcium concentration can cause hemodynamic instability.

In the present study we did not evaluate if these variations persist for more than 24 hours after dialysis. This will be the subject for a future study. Also, we would like to conduct a longitudinal study in order to evaluate the cumulative effect of the changes described in the present study.

Conclusions. Patients with ESRD undergoing hemodialysis are characterized by early arterial aging and an increase in cardiovascular morbidity and mortality. According to the present study, acute effects of hemodialysis do not alter significant the heart rate and blood pressure, but can cause significant changes in arterial stiffness.

SI measurement is an easy method to identify patients with increased arterial stiffness after dialysis.This type of acute postprocedural vascular response in patients with ESRD places them in a group with increased cardiovascular vulnerability.

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