The arterial stiffness changes in hemodialysis patients with chronic kidney disease: The impact on mortality

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Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2022;31(7):757–767

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Funding sources
None declared

Conflict of interest
None declared

Received on November 3, 2020
Reviewed on November 22, 2021
Accepted on February 26, 2022

Published online on April 8, 2022

Abstract

Background. Patients with kidney disease suffer from high cardiovascular risk due to classic and disease-specific risk factors. Arterial stiffness is a novel cardiovascular risk factor whose role is yet to be established. High-resolution echo-tracking is a developing method for the assessment of local arterial stiffness.

Objectives. To assess carotid stiffness in patients on long-term hemodialysis (HD) using high-resolution echo-tracking and to analyze the impact of arterial stiffness on mortality in the mid-term follow-up.

Materials and methods. Fifty-eight HD patients (28 female (F), 30 male (M)) underwent clinical examination, laboratory tests and carotid stiffness assessment. Local arterial stiffness parameters such as beta stiffness index (β), Young's modulus (Ep), arterial compliance (AC), and one-point pulse wave velocity (PWVβ) were measured both before and after HD, allowing to calculate their change (Δ). The survival of patients was analyzed up to 48 months. The multivariate analysis of survival with the use of Cox proportional hazard stepwise regression was performed to determine the factors significantly correlated with the survival.

Results. After 48 months, 33 patients were alive (16 F, 17 M) and 25 patients (12 F, 13 M) died. The deceased group was significantly older (66.5 ±12.3 years compared to 56.6 ±17.8 years), had more pronounced coronary artery disease (percutaneous coronary intervention (PCI) 36% compared to 9%, $p < 0.05$, respectively). Deceased patients had significantly higher ΔAC than survivors. The results showed that age, history of PCI, left ventricular ejection fraction (LVEF), ΔAC, fasting glucose, serum total protein, sodium level after HD, and potassium level before HD were significantly associated with mortality.

Conclusions. Echo-tracking-based arterial stiffness assessment in patients with chronic kidney disease (CKD) yields the clinical information regarding mid-term mortality risk. A paradoxical increase in AC is among independent risk factors for mid-term mortality in patients undergoing maintenance HD. The proper estimation of the correlations among vascular, hemodynamic and sympathetic-dependent changes in a given patient with kidney failure is complex.

Key words: hemodialysis, chronic kidney disease, arterial stiffness, mortality, echo-tracking

Cite as
Rekucki K, Sławuta A, Zyśko D, Madziarska K. The arterial stiffness changes in hemodialysis patients with chronic kidney disease: The impact on mortality. *Adv Clin Exp Med*. 2022;31(7):757–767. doi:10.17219/acem/146970

DOI
10.17219/acem/146970

Background

Cardiovascular diseases are the leading cause of death in patients with chronic kidney disease (CKD).[1] These patients suffer from high cardiovascular risk due to traditional and disease-specific risk factors. Arterial stiffness has been proven to be independently associated with a higher global risk of death in patients suffering from CKD.[2] The measurement of local arterial stiffness in CKD patients may be of particular value due to the limitations of classic diagnostic methods in this group of patients,[3,4] such as electrocardiographic exercise test or stress echocardiography.[5] These patients are less likely to have the classic symptoms of myocardial ischemia, hence the need to look for new tools to improve clinical evaluation. Damage to the kidneys also limits the possibility of using tests with contrast media – coronary angiography and computed tomography.[3] In this group of patients, the diagnostic value of laboratory exponents of cardiovascular function, such as N-terminal pro B-type natriuretic peptide (NT-proBNP) or cardiac troponin, is also lower.[6,7] Chronic kidney disease is affecting 10–16% of the world population.[8–10] As glomerular filtration rate (GFR) decreases, the likelihood of hypertension increases.[11] People with CKD are also characterized by an increased tendency to develop advanced atherosclerotic lesions.[12] It should be emphasized that the presence of classic cardiovascular risk factors such as diabetes, hypertension, nicotinism, and dyslipidemia does not sufficiently explain the clear increase in the risk of cardiovascular death in patients with CKD.[4,10]

Stiffness is one of the properties of arteries resulting from the vessel wall structure, in particular from the ratio of collagen to elastic fibers.[13,14] Left ventricular contraction causes an ejection of a certain volume of blood into the systemic circulation. The appearance of additional blood volume in the ascending aorta causes its distension, which is possible due to its high elasticity. This distension is then transferred to the distal parts of the arterial system, forming a pulse wave. The pulse wave, reaching the resistance vessels, is reflected due to the increase in the stiffness of arteries. The reflected wave returns to the ascending aorta in diastole, supporting coronary perfusion. The final shape of the pulse wave is therefore a result of a progressive wave and reflected wave. The increase in the stiffness of arteries, particularly in the aorta, leads to a shorter distance between the heart and the place where the reflected wave is formed, as well as to an increase in pulse wave speed. This causes many adverse effects on the cardiovascular system. The resulting reduction in diastolic blood pressure impairs coronary perfusion. At the same time, high central blood pressure leads to an increase in left ventricular afterload in the pressure overload mechanism. Therefore, an increase in arterial stiffness is a part of the development of hypertension, ischemic heart disease and heart failure.[15,16] Both aging and diseases such as essential hypertension, diabetes and CKD contribute to the increase in arterial stiffness.[17–19]

High-resolution echo-tracking is a direct and noninvasive method of the evaluation of local arterial stiffness. It is obtained by ultrasound examination at one point of the arterial system, usually at the site of the common carotid artery. According to experts from the European Society of Cardiology (ESC), it is recognized that methods for measuring local arterial stiffness, such as high-resolution echo-tracking, are useful in pathophysiology and therapy studies.[13] In recent years, the interest in using high-resolution echo-tracking in patients with CKD has increased.[20–22] There is growing evidence that carotid stiffness assessment may contribute to a better risk stratification of CKD patients. Studies have shown that carotid stiffness parameters obtained with high-resolution echo-tracking may be used in prediction of all-cause mortality in patients with kidney failure treated with hemodialysis (HD).[21]

Objectives

The aim of the study was to assess local arterial stiffness parameters in patients undergoing maintenance HD and relate these parameters to mortality in the mid-term follow-up.

Materials and methods

Study design and participants

This was a prospective cohort study. The analysis was performed in 58 patients (28 women and 30 men) with kidney failure treated with HD at Dialysis Center in Department of Nephrology and Transplantation Medicine (Wroclaw Medical University, Wrocław, Poland). Hemodialysis sessions were conducted 3 times a week for 4 h per session. The study group was formed in 2015 and patients were observed until 2019. The patients included in the study were free of active infection. We excluded patients with persistent or permanent atrial fibrillation, history of malignancy and diseases requiring immunosuppressive treatment.

All patients were treated with erythropoietin and intravenous iron supplementation according to standards. Beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, and alpha blockers were used in the treatment of hypertension. All patients were dialyzed using a native arteriovenous fistula.

The study was approved by Institutional Ethics Committee of the Wroclaw Medical University, Poland.

Variables and data sources

In all subjects, data on cardiovascular morbidity and causes of kidney failure were collected. Clinical data of patients were extracted from the hospital records.

At the study onset, the following factors were analyzed: baseline characteristics, duration of dialysis, adequacy of dialysis (Kt/V), body mass index (BMI), and laboratory parameters. Blood samples were collected prior to the initiation of HD session. Routine laboratory tests were measured in the Central Hospital Laboratory, University Hospital in Wrocław, Poland, as a part of the standard care.

Heart rate, blood pressure measurements and carotid elasticity with echo-tracking technique were investigated at the study onset, before and after a single midweek HD session. All patients underwent transthoracic echocardiogram.

Assessment of local arterial stiffness

Images were obtained with an Aloka Alpha 6 ultrasonograph (Aloka Co., Ltd., Tokyo, Japan) equipped with an integrated and automated Doppler and high-resolution echo-tracking system using a linear probe. Patients were examined in supine position 15 min before the start of HD and 15 min after the end of HD. A clear ultrasonographic visualization of both anterior and posterior wall of the common carotid artery opposite to the arteriovenous fistula was taken 1–2 cm below bifurcation in the longitudinal axis. Consequently, after establishing the intima-media complex, the echo-tracking samples were positioned at the end of intima, with an 1 kHz sampling rate for continuous detection of movement of the arterial wall. Thus, a graphical representation of change in the diameter of the artery was recorded as a waveform. Three to five evolutions were recorded to obtain a representative waveform.

To calculate local arterial stiffness parameters, it is necessary to register high-resolution echo-tracking, heart cycle and blood pressure. Heart cycle was recorded using standard electrocardiographic limb leads I, II and III. Blood pressure was measured over the brachial artery opposite the arteriovenous fistula in supine position, directly before the ultrasonographic examination.

As a result, the following parameters were calculated:

– β – beta stiffness index – ratio of the natural algorithm of systolic/diastolic blood pressure to the relative change in diameter:

$$\beta = \ln (Ps/Pd)/[(Ds - Dd)/Dd]$$

where: ln – the natural logarithm, Ps – systolic blood pressure, Pd – diastolic blood pressure, Ds – diameter of the artery in systole, Dd – diameter of the artery in diastole;

– Ep – epsilon, Young's modulus:

$$Ep = (Ps - Pd)/[(Ds - Dd)/Dd]$$

– AC – arterial compliance, calculated from the arterial cross-section and blood pressure:

$$AC = \pi(Ds \times Ds - Dd \times Dd)/[4 \times (Ps - Pd)]$$

– PWVβ – one-point pulse wave velocity, derived from the time delay between the 2 consecutive waveforms representing the diastole of the artery, with the use of beta stiffness index:

$$PWV\beta = \sqrt{(\beta \times Pd/2 \times r)}$$

where: β – beta stiffness index, Pd – diastolic blood pressure, r – blood density (1.050 kg/m^3).

The change (Δ) in carotid stiffness parameters was calculated as follows: Δβ = β after HD – β before HD; ΔEp = Ep after HD – Ep before HD; ΔAC = AC after HD – AC before HD; ΔPWVβ = PWVβ after HD – PWVβ before HD.

Statistical analyses

Statistical analyses were performed using STATISTICA v. 12 (TIBCO Software, Palo Alto, USA). Continuous variables were checked for the distribution using the Shapiro–Wilk W test and if the value of p was < 0.05, the assumption for normality was discarded. The Shapiro–Wilk W test showed normal distribution for the following variables: age, adequacy of HD, ultrafiltration during HD session, BMI, all echocardiographic parameters, echo tracking parameters except for Ep after HD, all blood pressure and heart rate parameters, and laboratory parameters except for fasting glucose, C-reactive protein (CRP) and high-density lipoprotein (HDL) cholesterol. Continuous variables with normal distribution were presented as means and standard deviations (SDs), and compared according to the survival groups (deceased compared to alive) with Student's t-test. Continuous variables without normal distribution were presented as medians and interquartile ranges (IQRs) and compared using Mann–Whitney U test. Discrete variables were presented as counts and percentages, and compared using χ^2 test. The comparison of the investigated parameters between the deceased patients depending on the causes of death (non-cardiovascular compared to cardiovascular mortality) was performed separately.

The multivariate survival analysis with the use of Cox proportional hazard stepwise regression was performed based on a model in which the dependent variable was the survival time since the inclusion in the study, while independent variables incorporated in the analysis were characteristics which differed in the one-way analysis with a significance of $p < 0.15$ between the 2 evaluated groups (survivors and non-survivors), or were relevant from the clinical point of view. In case of highly correlated variables such as heart rate before HD and heart rate after HD, serum total protein and serum total albumin, history of coronary artery disease and history of percutaneous coronary intervention (PCI), AC after HD and change in the arterial compliance (ΔAC), the more statistically significant variable was chosen. The following variables were considered for multivariate analysis: age, hypertension, history of PCI, left ventricular ejection fraction (LVEF), ΔAC, heart rate after HD, hemoglobin, serum total protein, fasting glucose, CRP, low-density lipoprotein (LDL) cholesterol, urea after HD, creatinine before HD, sodium level after HD, and potassium level before HD.

The survival analysis using Cox proportional hazard regression analysis was performed with the Cox proportional hazard analysis module. In the assumptions of the model, the reliability of Efron was selected, and models were created taking into account all effects and using the forward method. Then, Cox regression assumptions were assessed by analyzing Martingale-based residuals for survival models and Schoenfeld residuals over time, visually assessing a plot of the residuals compared to time. The correlation of residuals and time was examined using the Spearman's correlation. In case of finding a variable that violates the assumptions of the Cox proportional hazard regression, the variable was excluded from the model.

Receive operating characteristic (ROC) analysis was performed to find the cutoff point of echo-tracking parameters which differ between survivors and non-survivors. The Kaplan–Meier curve was constructed and the log-rank test was performed to present the survival in the groups of patients chosen on the basis of the founded cutoff points, as described above.

The multiple stepwise regression analysis was performed to find the association between echo-tracking parameters and age, gender, diabetes, and the presence of cardiovascular complications assessed as at least one of the following: previous myocardial infarction, stroke, history of coronary artery bypass graft surgery, or PCI. The variance inflation factor was assessed as the diagonal elements of the inverse correlation matrix. The Durbin–Watson test was performed to examine the autocorrelation of the residuals.

The results were considered statistically significant when the p-value was < 0.05.

Results

Clinical characteristics of the investigated patients at study onset are presented in Table 1.

Thirty-three patients from the initial cohort of 58 (56.89%) survived the whole 48-month observation period. Of the non-survivors, 11 patients (44%) died of cardiovascular diseases and 14 patients (56%) died of non-cardiovascular causes. The comparison of the investigated parameters between deceased and surviving patients is depicted in Table 2–4. The comparison of the investigated parameters between deceased patients depending on the causes (non-cardiovascular compared to cardiovascular mortality) is depicted in Table 5–7. The predictors of the overall mortality among the studied patients using Cox proportional hazards model are depicted in Table 8.

Based on the data obtained in the study, we created a multivariate analysis of survival with the use of Cox proportional hazard stepwise regression. The dependent variable was the survival of the whole 48-month observation period. Independent variables were: age, hypertension, history of PCI, LVEF, ΔAC, heart rate after HD, hemoglobin, fasting glucose, serum total protein, CRP, LDL cholesterol, urea after HD, creatinine before HD, sodium level after HD, and potassium level before HD. The stepwise forward model showed that factors which significantly correlated with survival were: age, history of PCI, LVEF, ΔAC, fasting glucose, serum total protein, sodium level after HD, and potassium level before HD.

In Fig. 1, a plot of Martingale-based residuals compared to survival time was depicted. In Table 9, the Spearman's correlation between Schoenfeld residuals of the model and survival time was shown.

The ROC curve analysis was performed to find the cutoff point between patients who survived the 48-month observation period and the deceased. In the Fig. 2, the ROC curve analysis for the ΔAC in survivors and non-survivors was presented. The cutoff point aimed at differentiating the groups was -0.06 mm^2/kPa. The area under curve was 0.71; 95% confidence interval (95% CI): [0.56; 0.85]; $p = 0.005$.

In Fig. 3, the crude Kaplan–Meier survival curves for the difference in survival regarding ΔAC for patients with $\Delta AC \geq -0.06$ and $\Delta AC < -0.06$ are presented. Patients with $\Delta AC \geq -0.06$ have worse outcome than patients with $\Delta AC < -0.06$. We assessed the significant cutoff point of survival as -0.06 mm^2/kPa.

The stepwise multivariate regression analysis revealed that age was only associated with β after HD, with Ep after HD and with PWVβ after HD. However, gender, diabetes

Table 1. Clinical characteristics of the investigated patients at study onset

Variables	
Age [years], mean (SD)	60.9 (±16.3)
Male gender, n (%)	30 (51.7)
Duration of HD therapy [months], median (IQR)	39 (13.7–85.4)
Adequacy of dialysis [Kt/V], mean (SD)	1.39 (±0.34)
Hypertension, n (%)	43 (74.1)
Diabetes mellitus, n (%)	22 (37.9)
BMI [kg/m^2], mean (SD)	25.9 (±5.4)
The cause of kidney failure	
Chronic glomerular disease, n (%)	18 (31)
Diabetic nephropathy, n (%)	5 (8.6)
Polycystic kidney disease, n (%)	5 (8.6)
Interstitial nephropathy, n (%)	7 (12.1)
Hypertensive nephropathy, n (%)	18 (31)
Other, n (%)	5 (8.6)
Cardiovascular morbidity	
Coronary artery disease, n (%)	25 (43.1)
Myocardial infarction, n (%)	9 (15.5)
PCI, n (%)	12 (20.7)
CABG, n (%)	5 (8.6)
Stroke, n (%)	10 (17.2)

SD – standard deviation; IQR – interquartile range; BMI – body mass index; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft; HD – hemodialysis.

Table 2. Comparison of the investigated parameters between deceased and surviving patients with kidney failure treated with HD – basic characteristics

Variables	Deceased n = 25	Surviving n = 33	p-value
Age [years], mean (SD)	66.5 (±12.3)	56.6 (±17.8)	0.021[t]
Male gender, n (%)	13 (52)	17 (51.5)	0.971
Duration of HD therapy [months], median (IQR)	46.9 (21–112.4)	33 (12–85)	0.236[u]
Adequacy of HD [Kt/V], mean (SD)	1.5 (±0.3)	1.4 (±0.4)	0.293[t]
Ultrafiltration during HD session [mL], mean (SD)	1792.0 (±922.4)	1692.4 (±786.4)	0.659[t]
Hypertension, n (%)	20 (80)	23 (69.7)	0.375
Diabetes mellitus, n (%)	12 (48)	10 (30.3)	0.169
BMI [kg/m^2], mean (SD)	25.2 (±6.1)	26.4 (±4.8)	0.410[t]
The cause of kidney failure			
Chronic glomerular disease, n (%)	6 (24)	12 (36.4)	0.314
Diabetic nephropathy, n (%)	3 (12)	2 (6.1)	0.745
Polycystic kidney disease, n (%)	0 (0)	5 (15.2)	0.118
Interstitial nephropathy, n (%)	4 (16)	3 (9.1)	0.694
Hypertensive nephropathy, n (%)	10 (40)	8 (24.2)	0.199
Other, n (%)	2 (8)	3 (9.1)	0.745
Cardiovascular morbidity			
Coronary artery disease, n (%)	14 (56)	11 (33.3)	0.084
Myocardial infarction, n (%)	6 (24)	3 (9.1)	0.235
PCI, n (%)	9 (36)	3 (9.1)	0.029
CABG, n (%)	3 (12)	2 (6.1)	0.745
Stroke, n (%)	4 (16)	6 (18.2)	0.894

[t] – variables compared using Student's t-test; [u] – variables compared using Mann–Whitney U test; other variables were compared using χ^2 test; SD – standard deviation; HD – hemodialysis; IQR – interquartile range; BMI – body mass index; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft.

Table 3. Comparison of the investigated parameters between deceased and surviving patients with kidney failure treated with HD – cardiological and vascular assessment

Variables	Deceased n = 25	Surviving n = 33	p-value
Echocardiographic features			
LVESd [mm], mean (SD)	35.0 (±7.3)	32.9 (±7.7)	0.311
LVEDd [mm], mean (SD)	53.6 (±7.3)	52.1 (±6.9)	0.420
LA diameter [mm], mean (SD)	42.6 (±6.9)	41.5 (±6.2)	0.517
Aortic diameter [mm], mean (SD)	33.6 (±4.8)	32.3 (±4.9)	0.352
IVSd [mm], mean (SD)	13.8 (±2.2)	13.2 (±2.3)	0.339
PWd [mm], mean (SD)	12.1 (±1.9)	11.5 (±1.4)	0.175
LVEF [%], mean (SD)	51.1 (±11.6)	57.5 (±9.1)	0.022
Echo-tracking parameters			
β before HD, mean (SD)	8.2 (±3.5)	8.7 (±4.5)	0.674
β after HD, mean (SD)	7.4 (±3.0)	8.1 (±3.8)	0.494
Δβ, mean (SD)	−1.4 (±3.6)	−1.4 (±3.6)	0.665
Ep [kPa] before HD, mean (SD)	117.4 (±58.5)	117.8 (±63.3)	0.979
Ep [kPa] after HD, mean (IQR)	96.0 (72.0–129.5)	94.5 (72.0–126.5)	0.920[u]
ΔEp [kPa], mean (SD)	−21.0 (±54.5)	−7.5 (±52.8)	0.376
AC [mm^2/kPa] before HD, mean (SD)	0.87 (±0.34)	0.78 (±0.33)	0.333
AC [mm^2/kPa] after HD, mean (SD)	1.04 (±0.42)	0.76 (±0.31)	0.007
ΔAC [mm^2/kPa], mean (SD)	0.22 (±0.29)	0.00 (±0.28)	<0.001
PWVβ [m/s] before HD, mean (SD)	6.1 (±1.5)	6.1 (±1.5)	0.854
PWVβ [m/s] after HD, mean (SD)	5.7 (±1.1)	6.0 (±1.4)	0.502
ΔPWVβ [m/s], mean (SD)	−0.2 (±1.3)	−0.4 (±1.3)	0.545
Blood pressure and heart rate			
SBP before HD [mm Hg], mean (SD)	144.8 (±22.6)	138.3 (±24.1)	0.320
SBP after HD [mm Hg], mean (SD)	133.3 (±21.0)	134.3 (±28.0)	0.887
DBP before HD [mm Hg], mean (SD)	73.6 (±11.4)	74.9 (±16.4)	0.762
DBP after HD [mm Hg], mean (SD)	74.8 (±13.7)	74.6 (±13.9)	0.949
Heart rate before HD, mean (SD)	78.2 (±14.6)	73.1 (±12.8)	0.066
Heart rate after HD, mean (SD)	81.0 (±13.9)	73.6 (±14.6)	0.066

[u] – variables compared using Mann–Whitney U test; other variables were compared using Student's t-test; LVESd – left ventricular end-systolic diameter; LVEDd – left ventricular end-diastolic diameter; LA – left atrium; IVSd – intraventricular septum thickness in diastole; PWd – posterior wall thickness in diastole; LVEF – left ventricular ejection fraction; SD – standard deviation; HD – hemodialysis; IQR – interquartile range; β – beta stiffness index; Ep – epsilon; AC – arterial compliance; PWVβ – one-point pulse wave velocity; SBP – systolic blood pressure; DBP – diastolic blood pressure.

and the presence of cardiovascular complications were not related to any parameters of arterial stiffness. The results of the stepwise multiple regression analyses were presented in Table 10–12.

Discussion

In the present study, we observed that the change in AC correlates with mid-term survival in patients undergoing maintenance HD. The AC is a parameter proportional to change in cross-sectional area of the artery, and inversely proportional to the change in blood pressure. In general population, the higher the AC, the more elastic the artery is. Previous studies have shown that the decrease in pulse pressure – which is a basic surrogate of arterial stiffness – after HD is connected with a longer survival of patients undergoing maintenance HD.[23] In contrary, the results of our study show that subjects with ΔAC equal or higher than −0.06 mm^2/kPa had shorter survival time in the mid-term follow-up than patients with ΔAC below the cutoff point. The Kaplan–Meier survival curves drifted apart after 600 days. Furthermore, the lone value of AC after HD was also correlated with worse outcome – survivors were characterized by a significantly lower AC after HD than deceased patients. We have not observed such correlation in AC before HD or for any other of the calculated carotid

Table 4. Comparison of the investigated parameters between deceased and surviving patients with kidney failure treated with HD – laboratory parameters

Variables	Deceased n = 25	Surviving n = 33	p-value
Hemoglobin [g/dL], mean (SD)	10.1 (±1.9)	11.1 (±4.1)	0.068
Serum total protein [g/dL], mean (SD)	6.7 (±0.7)	6.3 (±0.8)	0.068
Serum albumin [g/dL], mean (SD)	3.6 (±0.4)	3.8 (±0.5)	0.096
Fasting glucose [mg/dL], mean (IQR)	114.0 (91.0–168.0)	103.0 (90.0–131.0)	0.230[u]
CRP [mg/L], mean (IQR)	10.7 (3.9–28.3)	5.5 (3.4–10.6)	0.045[u]
Uric acid [mg/dL], mean (SD)	6.0 (±1.3)	6.4 (±1.6)	0.315
Total cholesterol [mg/dL], mean (SD)	177.2 (±42.1)	165.6 (±42.1)	0.366
HDL cholesterol [mg/dL], mean (IQR)	40.0 (34.0–46.9)	42.0 (36.0–50.0)	0.620[u]
LDL cholesterol [mg/dL], mean (SD)	102.0 (±42.3)	86.6 (±33.9)	0.131
Triglycerides [mg/dL], mean (SD)	189.6 (±143.3)	198.9 (±131.5)	0.800
Urea before HD [mg/dL], mean (SD)	114.8 (±28.2)	123.6 (±29.4)	0.256
Urea after HD [mg/dL], mean (SD)	34.6 (±13.1)	40.7 (±17.3)	0.149
Creatinine before HD [mg/dL], mean (SD)	7.0 (±2.4)	8.0 (±2.3)	0.073
Creatinine after HD [mg/dL], mean (SD)	3.0 (±1.3)	3.3 (±1.3)	0.238
Na^+ before HD [mmol/L], mean (SD)	136.8 (±3.3)	137.7 (±2.1)	0.246
Na^+ after HD [mmol/L], mean (SD)	136.5 (±1.3)	137.2 (±1.6)	0.057
K^+ before HD [mmol/L], mean (SD)	4.9 (±0.7)	5.3 (±0.7)	0.040
K^+ after HD [mmol/L], mean (SD)	4.0 (±0.4)	4.0 (±0.3)	0.756

[u] – variables compared using Mann–Whitney U test; other variables were compared using Student's t-test; HD – hemodialysis; CRP – C-reactive protein; HDL – high-density lipoprotein; LDL – low-density lipoprotein; SD – standard deviation; IQR – interquartile range.

Table 5. The comparison of the investigated parameters between deceased patients with kidney failure treated with HD depending on the causes (non-CV compared to CV mortality) – basic characteristics

Variables	Deceased non-CV mortality n = 14	Deceased CV-mortality n = 11	p-value
Age [years], mean (SD)	65.0 (±13.5)	68.4 (±10.9)	0.508[t]
Male gender, n (%)	7 (50.0)	6 (54.6)	0.859
Duration of HD therapy [months], median (IQR)	51.9 (20.1–68.3)	40.8 (21.3–114.2)	0.978[u]
Adequacy of HD [Kt/V], mean (SD)	1.4 (±0.3)	1.5 (±0.4)	0.620[t]
Ultrafiltration during HD session [mL], mean (SD)	1742.9 (±989.7)	1854.5 (±872.2)	0.771[t]
Hypertension, n (%)	11 (78.6)	9 (81.8)	0.763
Diabetes mellitus, n (%)	8 (57.1)	4 (36.4)	0.529
BMI [kg/m^2], mean (SD)	24.3 (±5.7)	26.3 (±6.5)	0.429[t]
The cause of kidney failure			
Chronic glomerular disease, n (%)	3 (21.4)	3 (27.3)	0.895
Diabetic nephropathy, n (%)	2 (14.3)	1 (9.1)	0.823
Polycystic kidney disease, n (%)	0 (0)	0 (0)	1.000
Interstitial nephropathy, n (%)	2 (14.3)	2 (18.2)	0.775
Hypertensive nephropathy, n (%)	6 (42.9)	4 (36.4)	0.742
Other, n (%)	1 (7.1)	1 (9.1)	0.573
Cardiovascular morbidity			
Coronary artery disease, n (%)	9 (64.3)	5 (45.6)	0.592
Myocardial infarction, n (%)	4 (28.6)	2 (18.2)	0.895
PCI, n (%)	7 (50)	2 (18.2)	0.220
CABG, n (%)	2 (14.3)	1 (9.1)	0.823
Stroke, n (%)	2 (14.3)	2 (18.1)	0.775

[t] – variables compared using Student's t-test; [u] – variables compared using Mann–Whitney U test; other variables were compared using χ^2 test; HD – hemodialysis; CV – cardiovascular; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft; SD – standard deviation; IQR – interquartile range; BMI – body mass index.

stiffness parameters. We hypothesize that in the group of patients with kidney failure, the pathophysiological process and degeneration of the arterial wall are so advanced that in most severe cases, the arteries lose ability to reduce inner diameter after dehydration during HD. This particular phenomenon may predict worse outcome.

There is some evidence stating that among patients with kidney failure treated with HD, a U-curve relationship between change in arterial stiffness and survival may occur. In one study, Lertdumrongluk et al. found that modest decline in pulse pressure, rather than either large reduction or rise in pulse pressure, is associated with the greatest survival.[24] This result may correspond with our findings, leading to a concept in which a potential significant decrease in arterial stiffness would correlate with a worse outcome.

In our study, we used high-resolution echo-tracking as a source of stiffness data. This method has already been used in studies on arterial stiffness in patients undergoing maintenance HD; however, only several of them focused on the role of carotid stiffness as a predictor of mortality in this group. Sato et al. found a correlation between high β and a higher risk of all-cause mortality in a 4-year follow up.[21] Another study on β has shown a predictive value of carotid stiffness on cardiovascular mortality independent of arterial thickness.[22] Blacher et al. investigated a potential role of the common carotid artery incremental

Table 6. The comparison of the investigated parameters between deceased patients with kidney failure treated with HD depending on the causes (non-CV compared to CV mortality) – cardiological and vascular assessment

Variables	Deceased non-CV mortality n = 14	Deceased CV-mortality n = 11	p-value
Echocardiographic features			
LVESd [mm], mean (SD)	35.2 (±7.3)	34.6 (±7.7)	0.848
LVEDd [mm], mean (SD)	52.8 (±6.5)	54.5 (±8.3)	0.580
LA diameter [mm], mean (SD)	43.9 (±7.9)	41.1 (±5.5)	0.328
Aortic diameter [mm], mean (SD)	35.1 (±4.9)	31.8 (±4.4)	0.102
IVSd [mm], mean (SD)	13.7 (±2.6)	13.8 (±1.8)	0.892
PWd [mm], mean (SD)	12.2 (±2.3)	12.0 (±1.3)	0.771
LVEF [%], mean (SD)	50.9 (±11.0)	51.4 (±12.9)	0.930
Echo-tracking parameters			
β before HD, mean (SD)	7.4 (±3.2)	9.1 (±3.8)	0.244
β after HD, mean (SD)	8.0 (±3.5)	6.6 (±1.9)	0.283
Δβ, mean (SD)	0.3 (±3.3)	−2.7 (±3.4)	0.053
Ep [kPa] before HD, mean (SD)	104.8 (±47.8)	131.2 (±67.8)	0.289
Ep [kPa] after HD, mean (SD)	104.4 (±44.9)	92.0 (±30.6)	0.457
ΔEp [kPa], mean (SD)	−2.6 (±44.2)	−43.0 (±59.7)	0.083
AC [mm^2/kPa] before HD, mean (SD)	0.87 (±0.32)	0.87 (±0.38)	0.986
AC [mm^2/kPa] after HD, mean (SD)	1.04 (±0.47)	1.03 (±0.37)	0.962
ΔAC [mm^2/kPa], mean (SD)	0.27 (±0.27)	0.16 (±0.31)	0.388
PWVβ [m/s] before HD, mean (SD)	5.8 (±1.5)	6.4 (±1.6)	0.401
PWVβ [m/s] after HD, mean (SD)	5.7 (±1.2)	5.7 (±0.9)	0.968
ΔPWVβ [m/s], mean (SD)	−0.1 (±1.2)	−0.8 (±1.4)	0.222
Blood pressure and heart rate			
SBP before HD [mm Hg], mean (SD)	144.2 (±24.8)	145.5 (±21.1)	0.895
SBP after HD [mm Hg], mean (SD)	133.5 (±20.5)	133.0 (±28.9)	0.960
DBP before HD [mm Hg], mean (SD)	75.5 (±13.3)	71.8 (±9.3)	0.466
DBP after HD [mm Hg], mean (SD)	71.2 (±13.9)	79.5 (±12.6)	0.155
Heart rate before HD, mean (SD)	83.6 (±13.0)	71.2 (±14.1)	0.031
Heart rate after HD, mean (SD)	83.1 (±13.7)	78.3 (±14.3)	0.425

variables were compared using Student's t-test; CV – cardiovascular; LVESd – left ventricular end-systolic diameter; LVEDd – left ventricular end-diastolic diameter; LA – left atrium; IVSd – intraventricular septum thickness in diastole; PWd – posterior wall thickness in diastole; LVEF – left ventricular ejection fraction; HD – hemodialysis; β – beta stiffness index; Ep – epsilon; AC – arterial compliance; PWVβ – one-point pulse wave velocity; SBP – systolic blood pressure; DBP – diastolic blood pressure; SD – standard deviation.

Table 7. The comparison of the investigated parameters between deceased patients with kidney failure treated with HD depending on the causes (non-CV compared to CV mortality) – laboratory parameters

Variables	Deceased non-CV mortality n = 14	Deceased CV-mortality n = 11	p-value
Hemoglobin [g/dL], mean (SD)	9.6 (±1.6)	10.7 (±2.1)	0.156
Serum total protein [g/dL], mean (SD)	6.6 (±0.7)	6.8 (±0.7)	0.515
Serum albumin [g/dL], mean (SD)	3.5 (±0.5)	3.6 (±0.3)	0.773
Fasting glucose [mg/dL], mean (SD)	145.1 (±61.9)	141.6 (±99.1)	0.915
CRP [mg/L], mean (SD)	16.0 (±18.2)	31.8 (±48.0)	0.267
Uric acid [mg/dL], mean (SD)	5.9 (±1.3)	6.1 (±1.2)	0.699
Total cholesterol [mg/dL], mean (SD)	175.7 (±66.6)	179.2 (±39.1)	0.880
HDL cholesterol [mg/dL], mean (SD)	42.9 (±13.4)	40.5 (±12.7)	0.657
LDL cholesterol [mg/dL], mean (SD)	97.9 (±51.0)	107.2 (±29.4)	0.595
Triglycerides [mg/dL], mean (SD)	169.4 (±113.7)	215.5 (±176.6)	0.595
Urea before HD [mg/dL], mean (SD)	118.0 (±22.9)	110.6 (±34.4)	0.528
Urea after HD [mg/dL], mean (SD)	36.2 (±12.6)	32.5 (±14.0)	0.497
Creatinine before HD [mg/dL], mean (SD)	6.9 (±2.3)	7.0 (±2.1)	0.871
Creatinine after HD [mg/dL], mean (SD)	3.0 (±1.3)	2.9 (±1.3)	0.934
Na^+ before HD [mmol/L], mean (SD)	136.6 (±2.9)	137.1 (±3.8)	0.740
Na^+ after HD [mmol/L], mean (SD)	136.5 (±1.3)	136.5 (±1.3)	0.933
K^+ before HD [mmol/L], mean (SD)	4.8 (±0.7)	5.0 (±0.50	0.505
K^+ after HD [mmol/L], mean (SD)	4.0 (±0.5)	4.0 (±0.4)	0.980

variables were compared using Student's t-test; CV – cardiovascular; HD – hemodialysis; CRP – C-reactive protein; HDL – high-density lipoprotein; LDL – low-density lipoprotein; SD – standard deviation.

modulus of elasticity (E_{inc}), showing that E_{inc} is an independent predictor of both cardiovascular and all-cause mortality in patients with kidney failure treated with HD.[25] In contrary to these studies, we explored a wider spectrum of carotid stiffness parameters directly before and after HD. To the best of our knowledge, there are no studies exploring the potential predictive value of change in these particular arterial stiffness parameters during a single HD session.

Apart from the findings considering arterial stiffness, our study has shown the association between the cardiological burden and survival of patients with kidney failure. Deceased patients had lower LVEF and more often

Table 8. Predictors of overall mortality among patients with kidney failure treated with HD using Cox proportional hazards model

Variables	Full model		Multivariate adjusted HR	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age [years]	1.184 [1.054; 1.331]	0.004	1.129 [1.054; 1.209]	0.001
PCI	77.697 [5.900; 1023.153]	0.001	11.123 [2.245; 55.114]	0.003
LVEF [%]	1.110 [0.995; 1.238]	0.061	1.079 [1.007; 1.157]	0.031
ΔAC [mm^2/kPa]	4687.865 [20.887; 1,052,157.000]	0.002	221.957 [11.250; 4379.027]	<0.001
Fasting glucose [mg/dL]	0.990 [0.980; 1.000]	0.027	0.989 [0.981; 0.998]	0.013
Serum total protein [g/dL]	5.513 [1.581; 19.228]	0.007	5.521 [2.218; 13.744]	<0.001
Na^+ after HD [mmol/L]	0.365 [0.163; 0.816]	0.014	0.430 [0.243; 0.762]	0.004
K^+ before HD [mmol/L]	0.166 [0.023; 1.213]	0.077	0.142 [0.041; 0.487]	0.002
Hypertension	0.387 [0.059; 2.549]	0.324	N/A	N/A
Heart rate after HD	1.012 [0.965; 1.062]	0.623	N/A	N/A
Hemoglobin [g/dL]	0.646 [0.438; 0.953]	0.027	N/A	N/A
CRP [mg/L]	1.026 [0.998; 1.054]	0.065	N/A	N/A
LDL cholesterol [mg/dL]	1.029 [1.006; 1.053]	0.013	N/A	N/A
Urea after HD [mg/dL]	0.968 [0.916; 1.062]	0.250	N/A	N/A
Creatinine before HD [mg/dL]	0.997 [0.683; 1.454]	0.986	N/A	N/A

R^2 = 0.84; HR – hazard ratio; 95% CI – 95% confidence interval; PCI – percutaneous coronary intervention; LVEF – left ventricular ejection fraction; AC – arterial compliance; HD – hemodialysis; CRP – C-reactive protein; LDL – low-density lipoprotein; N/A – not applicable.

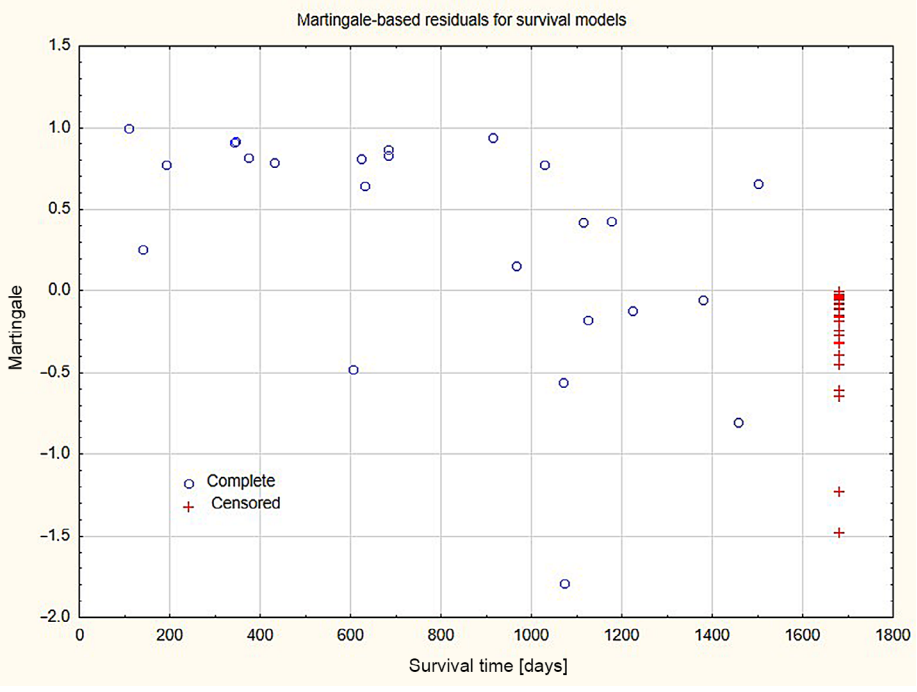

Fig. 1. Martingale-based residuals for survival models

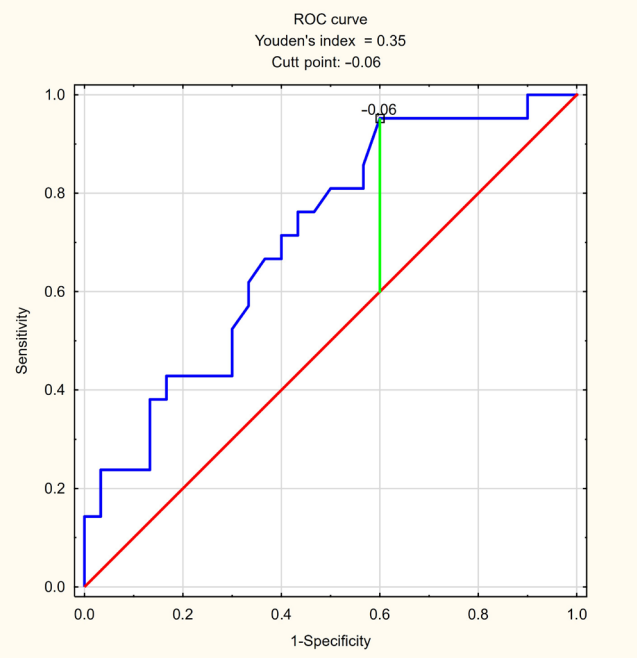

Fig. 2. Receiver operating characteristic (ROC) curve. The change in arterial compliance (ΔAC) in survivors and non-survivors

Table 9. Spearman's correlations between Schoenfeld residuals and survival

Schoenfeld residual	R Spearman	p-value
Schoenfeld residual for LVEF	0.12	0.599
Schoenfeld residual for Na^+ after HD	0.16	0.497
Schoenfeld residual for K^+ before HD	0.13	0.583
Schoenfeld residual for serum total protein	−0.40	0.069
Schoenfeld residual for PCI	−0.14	0.531
Schoenfeld residual for age	0.04	0.857
Schoenfeld residual for fasting glucose	−0.23	0.319
Schoenfeld residual for ΔAC	0.26	0.251

LVEF – left ventricular ejection fraction; HD – hemodialysis; PCI – percutaneous coronary intervention; AC – arterial compliance.

had a history of PCI, which are the results of heart failure and coronary artery disease (CAD), respectively. Also, the deceased patients were characterized by a lower serum potassium level, which may be related to a higher risk of tachyarrhythmias.

The assessment of hemodynamic changes in patients with kidney failure is not a simple task. It should be taken

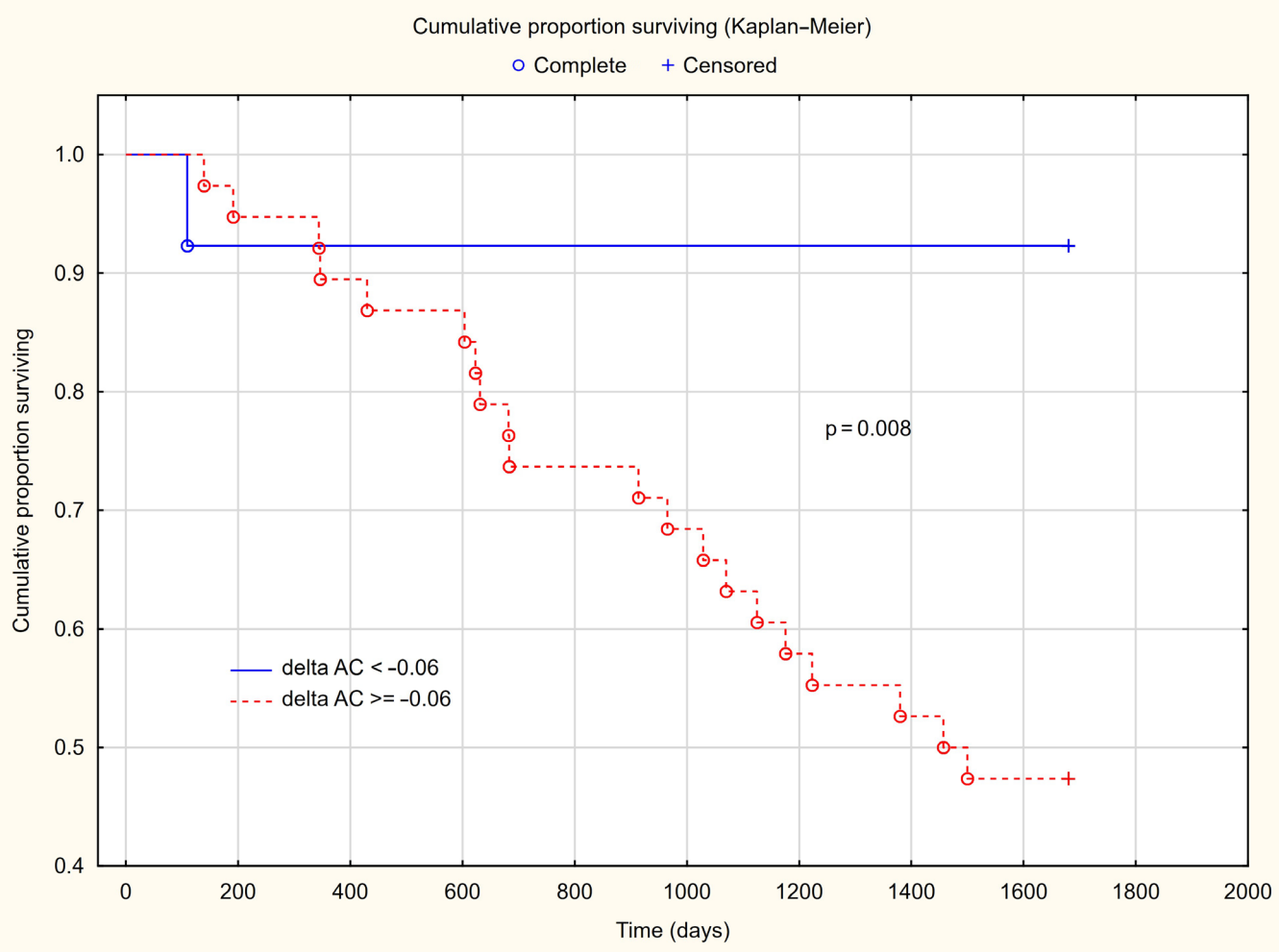

Fig. 3. Kaplan–Meier survival curves. Survival of patients regarding the change in arterial compliance (ΔAC) for patients with ΔAC ≥ −0.06 mm^2/kPa and ΔAC < −0.06 mm^2/kPa

Table 10. Stepwise multiple regression analysis for the association between a dependent variable β and age, gender, diabetes, and the presence of CV complications (at least one of the following: previous MI, stroke, CABG, PCI) in patients with kidney failure treated with HD

Variable	BETA	SE BETA	b	SE b	p-value
Age	0.36	0.13	0.07	0.03	<0.007

$R^2 = 0.13$; adjusted $R^2 = 0.11$; $p < 0.007$. Age was not associated with the remaining echo-tracking parameters. Gender, diabetes and the presence of CV complications were not associated with echo-tracking parameters. Variance inflation factor was less than 2 for all analyses, and the Durbin–Watson test was between 2.4 and 2.5. SE – standard error; BETA – standardized regression coefficients; b – raw regression coefficients; R^2 – coefficient of determination; adjusted R^2 – adjusted coefficient of determination; β – beta stiffness index; HD – hemodialysis; CV – cardiovascular; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft; MI – myocardial infarction.

Table 11. Stepwise multiple regression analysis for the association between a dependent variable Ep and age, gender, diabetes, and the presence of CV complications (at least one of the following: previous MI, stroke, CABG, PCI) in patients with kidney failure treated with HD

Variable	BETA	SE BETA	b	SE b	p-value
Age	0.42	0.12	1.32	0.39	<0.002

$R^2 = 0.17$; adjusted $R^2 = 0.16$; $p < 0.002$. Age was not associated with the remaining echo-tracking parameters. Gender, diabetes and the presence of CV complications were not associated with echo-tracking parameters. Variance inflation factor was less than 2 for all analyses, and the Durbin–Watson test was between 2.4 and 2.5. SE – standard error; BETA – standardized regression coefficients; b – raw regression coefficients; R^2 – coefficient of determination; adjusted R^2 – adjusted coefficient of determination; Ep – epsilon; HD – hemodialysis; CV – cardiovascular; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft; MI – myocardial infarction.

Table 12. Stepwise multiple regression analysis for the association between a dependent variable PWVβ and age, gender, diabetes, and the presence of CV complications (at least one of the following: previous MI, stroke, CABG, PCI) in patients with kidney failure treated with HD

Variable	BETA	SE BETA	b	SE b	p-value
Age	0.36	0.13	0.03	0.01	<0.006

$R^2 = 0.13$; adjusted $R^2 = 0.12$; $p < 0.006$. Age was not associated with the remaining echo-tracking parameters. Gender, diabetes and the presence of CV complications were not associated with echo-tracking parameters. Variance inflation factor was less than 2 for all analyses, and the Durbin–Watson test was between 2.4 and 2.5. SE – standard error; BETA – standardized regression coefficients; b – raw regression coefficients; R^2 – coefficient of determination; adjusted R^2 – adjusted coefficient of determination; PWVβ – one-point pulse wave velocity; HD – hemodialysis; CV – cardiovascular; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft; MI – myocardial infarction.

into account, that changes in stiffness parameters during HD may indicate both pathological changes in the vessels themselves and unfavorable processes in the autonomic system. Some blood pressure changes are provoked by higher fluid or sodium removal. On the other hand, cardiovascular changes can be disturbed in the state of raised sympathetic tone present in CKD patients.[26] Sympathetic hyperactivity is taken into account as one of the reasons of intradialytic blood pressure changes.[27] The hydration status may also be considered a factor impacting arterial stiffness. In a study on a group of HD patients, hypervolemia (assessed as left ventricle end-diastolic volume) was significantly associated with pulse pressure.[28] Moreover, it cannot be ruled out that the increase in AC after HD is a result of decrease in systolic blood pressure following dehydration. Hemodialysis may impact local arterial stiffness in a complex mechanism, in which the decrease of blood pressure, dehydration and individual properties of the cardiovascular system overlap and lead to the change in AC. This reaction of cardiovascular system is correlated with the survival.

The correlation with mortality of other echo-tracking parameters such as β, Ep and PWVβ remained statistically insignificant both before and after the HD, which stays in opposition to the previous findings.[21,22] Because of the existing shortage in the studies on the abovementioned parameters in kidney failure patients, with regard to all-cause mortality, and in particular cardiovascular mortality, the discussion of those relationships would be complex or probabilistic one.

Clinical implications

Our study shows that high-resolution echo-tracking may provide a unique insight into pathophysiology of cardiovascular disease in patients with kidney failure, and particularly, in patients treated with maintenance HD. It also gives hope for a better risk stratification among those patients. Further pathophysiological studies will be needed in order to recognize the underlying cause of paradoxical change in AC and a potential utility of this phenomenon. Moreover, further studies are required to establish how to control arterial stiffness in order to improve the outcomes.

Limitations

Our study has several limitations. It was observational in nature and thus, the causality could not be directly derived from the results. It had also a relatively small number of participants. The mid-term follow-up of 48 months seems to be also a limitation. Nevertheless, the subject did not undergo extensive investigations, so our study adds an important piece of data regarding the studied issue.

Conclusions

Echo-tracking-based arterial stiffness assessment in patients with CKD yields the clinical information regarding mid-term mortality risk. The independent risk factors for mid-term mortality in patients with kidney failure treated with HD are age, PCI, LVEF, ΔAC, fasting glucose, serum total protein, sodium level after HD, and potassium level before HD. The proper estimation of the correlations among vascular, hemodynamic and sympathetic-dependent changes in a given patient with kidney failure is complex.

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