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Comparison of aortic pressures and aortic elastic properties between patients with end-stage renal disease and healthy controls

MACİT KALÇIK[1,*], MUCAHİT YETİM[1], TOLGA DOĞAN[1], İBRAHİM DOĞAN[2], BARIŞ ESER[2], LÜTFÜ BEKAR[1], OĞUZHAN ÇELİK[3], YUSUF KARAVELİOĞLU[1]

[1]Department of Cardiology, Faculty of Medicine, Hitit University, Çorum, Turkey
[2]Department of Nephrology, Faculty of Medicine, Hitit University, Çorum, Turkey
[3]Department of Cardiology, Muğla Sıtkı Koçman University Training and Research Hospital, Muğla, Turkey
*Corresponding author: Macit Kalçık, MD; Department of Cardiology, Faculty of Medicine, Hitit University, Buharaevler Mah. Buhara 25. Sok. No: 1, A Daire: 22, Çorum, Turkey; Phone: +90 536 492 17 89; Fax: 90 364 511 78 89; E-mail: macitkalcik@yahoo.com

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Abstract: *Background:* Current evidence indicates that vascular calcification plays an essential role in the development of cardiovascular diseases in end-stage renal disease (ESRD) patients. Arterial stiffness is a marker of increased cardiovascular risk in various populations. The aim of this study is to evaluate the elastic properties of ascending aorta in patients with ESRD. *Methods:* This single-center study enrolled 96 patients (45 females, age: 57.2 ± 12.8 years) with ESRD and 96 healthy controls (52 females, age: 55.3 ± 10.1 years). Aortic pressures and aortic elastic parameters including aortic strain, aortic distensibility, aortic stiffness index, and aortic compliance were calculated using accepted formulae. *Results:* The hemodynamic parameters including aortic pulse pressure, aortic mean pressure, aortic fractional pulse pressure, and aortic pulsatility index were significantly higher in patients with ESRD. Systolic and diastolic aortic diameters were similar between the groups. However, pulsatile aortic diameter change, aortic strain, aortic distensibility, and aortic compliance were significantly lower, whereas aortic stiffness index was significantly higher in ESRD group. *Conclusions:* The results demonstrated that a significant difference was present in terms of aortic blood pressures between patients with ESRD and controls. In addition, the elastic properties of ascending aorta were decreased in patients with ESRD.

Keywords: aortic stiffness index, aortic strain, end-stage renal disease, echocardiography, hypertension

Introduction

Cardiovascular disease is the most common cause of morbidity and mortality among patients with end-stage renal disease (ESRD). Accelerated arteriosclerosis has been well-established in patients with ESRD with much higher incidence than those in the general population even after adjustment for traditional cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidemia [1]. The underlying mechanisms, which are responsible for progression of cardiovascular diseases, have not been clearly defined; however, the contribution of inflammation, oxidative stress, endothelial dysfunction, and dysregulated mineral metabolism has been reported previously [2]. Current evidence indicates that vascular calcification plays an essential role in the development of cardiovascular diseases in ESRD patients. Calcification of the vascular smooth muscle cells results in increased arterial stiffness that causes systolic hypertension, left ventricular hypertrophy, and reduced coronary perfusion [3].

Aortic stiffness is defined as the arterial rigidity caused by the loss of elastic tissue in the arterial wall that decreases the widening capacity of the artery. The pathogenesis is a complex process that involves the alteration of elastin and collagen in the vascular wall and endothelial dysfunction accompanied by inflammation and oxidative stress [4]. Arterial stiffness is a marker of increased cardiovascular risk and a predictor for cardiovascular morbidity and mortality in various populations [5]. Non-invasive assessment of aortic elastic properties may

provide a method for early detection of atherosclerotic changes. Many different indices have been developed for proper estimation of arterial stiffness, such as aortic strain, distensibility, compliance, and stiffness index [6–8].

We hypothesized that vascular calcification in patients with ESRD may also play major role in the development of aortic atherosclerosis and increased aortic stiffness. In this study, we aimed to evaluate the elastic properties of ascending aorta in patients with ESRD.

Material and Methods

Study population

This single-center study enrolled 96 patients (45 females, mean age: 57.2 ± 12.8 years) with ESRD (glomerular filtration rate <15 ml/min/1.73 m^2), along with 96 healthy controls (52 females, mean age: 55.3 ± 10.1 years). Patients diagnosed with coronary artery disease, history of myocardial infarction, left ventricular dysfunction [left ventricular ejection fraction (LVEF) <50%), severe heart valve disease, cardiomyopathy, arrhythmia, active infection, connective tissue disease, and liver or thyroid dysfunction were excluded from the study. All patients underwent transthoracic echocardiography (TTE). Complete blood count and blood chemistry tests were performed in all patients during admission. All demographic, laboratory, and echocardiographic parameters were recorded into a data set and compared between ESRD patients and controls. All patients provided a written informed consent and the study protocol was approved by the local ethics committee of the hospital in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Echocardiography

All patients were evaluated by TTE, which was performed using a 3.2 MHz adult probe on a Vivid 5 echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway) in the left lateral decubitus position. Parasternal long-axis and short-axis views and apical two, four, and five chamber views were used during TTE evaluation. In all patients, left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal thickness (IVST), and posterior wall thickness (PWT) were measured on the parasternal long-axis view. LVEF was calculated using biplane Simpson's method.

Laboratory analysis

In order to perform complete blood count and blood chemistry panel, venous blood samples were collected after 12 h of fasting by a clean puncture of an antecubital vein from all patients. Complete blood countings were measured on Sysmex XT2000i analyzer (Sysmex Corporation, Kobe, Japan). Fasting blood glucose, urea, creatinine, sodium, potassium, calcium, phosphorus, uric acid, total cholesterol (TC), high-density lipoprotein (HDL), and triglyceride (TG) levels were also measured on an autoanalyzer (Siemens Advia 2400 Chemistry System, Siemens Diagnostic, Tarrytown, NY, USA). Low-density lipoprotein (LDL) was calculated using the Friedewald formula [LDL (mg/dl) = TC − (HDL + TG/5)] [9]. The glomerular filtration rate was calculated as a function of age, serum creatinine, and race using the simplified modified diet in renal disease equation [10].

Measurement of aortic pressures

All patients had blood pressure measured prior to echocardiographic assessment. Aortic pressure measurements were performed while the patients were sitting comfortably on a chair with their feet resting on the floor using a sphygmomanometer with an appropriately sized cuff (wrapping at least 80% of the forearm). Blood pressure measurements were recorded 12 h after the last administration of a vasoactive drug or alcohol consumption and after 3 h of abstinence of caffeine and tobacco. Patients rested 10 min in a supine position in a quiet room at a temperature of 20–22 °C before measurements were taken. During measurements, the average of at least three measurements was taken into consideration for analysis of systolic (SBP) and diastolic blood pressures (DBP).

Calculation of hemodynamic parameters was performed using the formulas below:

- Aortic pulse pressure = SBP − DBP
- Aortic mean pressure = [SBP + (DBP × 2)]/3
- Aortic fractional pulse pressure = Aortic pulse pressure/Aortic mean pressure
- Aortic pulsatility index = Aortic pulse pressure/DBP

Measurement of aortic elastic properties

Aortic systolic (ASD) and diastolic diameters (ADD) were assessed on the basis of a 2D-guided M-mode recording of the proximal ascending aorta, defined as 3 cm above the aortic valve in the parasternal long-axis view with TTE. ASD was measured at the time of full opening of the aortic valve, and ADD was measured at the peak of the R wave of the simultaneously recorded electrocardiogram; five measurements were averaged for each diameter. Aortic elastic parameters including aortic strain, aortic distensibility, aortic stiffness index, and aortic compliance were calculated using the formulae below:

- Aortic strain (%) = 100 × [(ASD − ADD)/ADD]
- Aortic distensibility (10^{-6} cm^2 dyn^{-1}) = (2 × Aortic strain)/[100 × (SBP − DBP)]

- Aortic stiffness index = Logarithm [100 × (SBP/DBP)/Aortic strain]
- Aortic compliance (cm/mmHg) = (ASD – ADD)/(SBP – DBP)

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0. (IBM Corp., Armonk, NY, USA). The variables were investigated using analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) to determine whether or not they were approximately normally distributed. Descriptive statistics were reported as mean with standard deviation for continuous variables with normal distribution, median and 25th–75th percentile values for continuous variables without normal distribution, and frequencies with percentages for the categorical variables. Group comparisons for continuous variables were tested using Student's *t*-test when data distribution was normal and using Mann–Whitney *U* test when data distributions were not normal. Comparisons for categorical variables were evaluated by χ^2 test. Significance level was accepted as $p < 0.05$ in all statistical analyses.

Results

The clinical and demographical characteristics of patients with ESRD and controls were presented in *Table I*. There was no significant difference between the groups in terms of age, gender, body mass index, and heart rate. The frequencies of diabetes mellitus and hypertension, SBP, and DBP were significantly higher in patients with ESRD.

Upon comparison of laboratory parameters between ESRD group and controls, there was no significant difference in terms of white blood cells, platelets, fasting blood glucose, and uric acid between the groups. However, hemoglobin, glomerular filtration rate, TC, HDL, LDL, sodium, calcium, and albumin levels were significantly lower in ESRD group. On the other hand, urea, creatinine, TG, potassium, and phosphorus levels were significantly higher in patients with ESRD as compared to controls *(Table I)*.

A significant difference was present in terms of echocardiographic parameters related to left ventricular hypertrophy and left atrial dilatation between patients with ESRD and controls. LAD, LVEDD, LVESD, IVST, and PWT were significantly higher, whereas LVEF was significantly lower in patients with ESRD *(Table I)*.

The hemodynamic parameters of aorta were compared between groups. Aortic pulse pressure (51.4 ± 13.9 vs. 41.8 ± 8.1 mmHg; $p < 0.001$), aortic mean pressure (101.2 ± 16.1 vs. 90.2 ± 8.8 mmHg; $p < 0.001$), aortic fractional pulse pressure (0.51 ± 0.12 vs. 0.46 ± 0.09; $p = 0.005$), and aortic pulsatility index (0.62 ± 0.18 vs. 0.55 ± 0.13; $p = 0.004$) were significantly higher in patients with ESRD as compared to controls *(Table II)*.

Elastic properties of ascending aorta were also compared between the groups. ASD (33.1 ± 3.9 vs. 33.7 ± 3.8 mm; $p = 0.426$) and ADD (31.1 ± 4.3 vs. 30.9 ± 3.8 mm; $p = 0.646$) were similar between patients with ESRD and controls. However, pulsatile aortic diameter change (2.07 ± 1.17 vs. 2.81 ± 0.98 mm; $p < 0.001$), aortic strain (7.55 ± 5.27 vs. $9.97\% \pm 4.17\%$; $p < 0.001$), aortic distensibility (7.63 ± 5.75 vs. 8.41 ± 4.19 10^{-6} cm^2 dyn^{-1}; $p < 0.001$), and aortic compliance (0.043 ± 0.035 vs. 0.069 ± 0.028; $p < 0.001$) were significantly lower in ESRD group. Whereas aortic stiffness index (3.24 ± 0.59 vs. 2.80 ± 0.34; $p < 0.001$) was significantly higher in patients with ESRD *(Table II; Fig. 1)*.

Discussion

In this study, we aimed to evaluate the elastic properties of ascending aorta in patients with ESRD. A significant difference was present in terms of aortic blood pressures and echocardiographic parameters related to left ventricular hypertrophy and left atrial dilatation between groups. Furthermore, the elastic properties of ascending aorta were decreased and aortic stiffness was increased in patients with ESRD as compared to healthy controls.

Chronic kidney disease is strongly associated with increased incidence of cardiovascular diseases, and patients with ESRD are 10–20 times more likely to die from cardiovascular events than the general population [11]. Cardiovascular risk factors such as diabetes mellitus, hypertension, and dyslipidemia are more prevalent in patients with ESRD; however, their presence alone does not explain this excess risk of cardiovascular events [12]. The failure of traditional risk factors to explain the increased cardiovascular risk of ESRD patients has led to growing interest in non-traditional risk factors, such as arterial stiffness, inflammation, and endothelial dysfunction [13, 14].

Aortic stiffness describes the elastic resistance that the aorta sets against its distension. In addition to being a blood carrying elastic artery, the aorta has important effects on left ventricular functions and coronary blood flow. Furthermore, increased arterial stiffness causes the early reflection of pulse wave and increases blood pressure and left ventricular afterload [15]. Arterial stiffness has been recognized as an important risk factor for cardiovascular events in patients with chronic kidney disease, especially those with ESRD. The significance of the elastic features of vascular structures has been recognized in the development of atherosclerosis, and is considered to be a factor causing atherosclerosis [16].

It was demonstrated that increased aortic stiffness and low aortic distensibility are indicators of impairment of the elastic structure of the aorta and associated with

Table I Baseline characteristics of the study groups

	ESRD ($n=96$)	Controls ($n=96$)	p value
Demographic parameters			
Age (years)	57.2 ± 12.8	55.3 ± 10.1	0.231
Gender [female, n (%)]	45 (46.9)	52 (54.2)	0.312
Body mass index (kg/m^2)	27.9 ± 4.7	28.6 ± 3.6	0.388
Hypertension [n (%)]	72 (75)	0 (0)	<0.001
Diabetes mellitus [n (%)]	26 (27.1)	0 (0)	<0.001
Systolic blood pressure (mmHg)	135.5 ± 21.9	118.2 ± 11.3	<0.001
Diastolic blood pressure (mmHg)	84.1 ± 14.4	76.2 ± 8.6	<0.001
Heart rate (beats/min)	79.7 ± 14.7	77.1 ± 12.2	0.252
Laboratory parameters			
WBC (×103/ml)	6.6 ± 1.9	7.1 ± 1.9	0.089
Hemoglobin (g/dl)	12.5 ± 1.7	14.3 ± 1.5	<0.001
Platelet (×10^3 cells/dl)	224 ± 58	238 ± 63	0.145
Glucose (mg/dl)	114.7 ± 56.6	108.4 ± 34.2	0.348
BUN (mg/dl)	52.4 ± 15.2	13.5 ± 3.8	<0.001
Creatinine (mg/dl)	6.9 ± 1.8	0.7 ± 0.1	<0.001
GFR (ml/min/1.73 m^2)	8.2 ± 2.3	105.8 ± 12.5	<0.001
Sodium (mEq/L)	137.3 ± 2.7	139.4 ± 2.1	<0.001
Potassium (mEq/L)	4.9 ± 0.6	4.4 ± 0.3	<0.001
Calcium (mg/dl)	8.9 ± 0.9	9.4 ± 0.4	<0.001
Phosphorus (mg/dl)	4.5 ± 1.3	3.3 ± 0.5	<0.001
Albumin (g/dl)	4.1 ± 0.4	4.4 ± 0.3	<0.001
Uric acid (mg/dl)	4.9 ± 1.3	4.8 ± 1.3	0.696
Total cholesterol (mg/dl)	185.7 ± 49.2	209.9 ± 41.2	<0.001
High-density lipoprotein (mg/dl)	39.7 ± 12.3	45.3 ± 12.9	0.002
Low-density lipoprotein (mg/dl)	104.7 ± 36.8	133.4 ± 35.7	<0.001
Triglyceride (mg/dl)	156 (113–257)	136 (89–202)	0.022
Echocardiographic parameters			
Left atrial diameter (mm)	36.3 ± 5.3	32.6 ± 3.6	<0.001
LV ejection fraction (%)	59.8 ± 7.3	62.3 ± 5.8	0.009
LV end-diastolic diameter (mm)	47.7 ± 6.1	43.6 ± 5.3	<0.001
LV end-systolic diameter (mm)	31.8 ± 6.1	28.9 ± 5.9	0.001
Interventricular septal thickness (mm)	11.9 ± 2.1	10.2 ± 1.8	<0.001
Posterior wall thickness (mm)	11.7 ± 1.9	10.1 ± 1.7	<0.001

BUN: blood urea nitrogen; ESRD: end-stage renal disease; GFR: glomerular filtration rate; LV: left ventricle; WBC: white blood cell

coronary artery disease [17]. Atherosclerotic changes in arterial wall include smooth muscle cell proliferation, deposition of lipid, and accumulation of collagen, elastin, and proteoglycans, which have been known to structurally affect the elastic behavior of arterial walls [18]. A positive correlation has been reported between the amount of severity of atherosclerosis in the coronary bed and the aorta or its major branches [19]. Furthermore, vascular calcification results in increased arterial stiffness and plays an essential role in the development of cardiovascular diseases in ESRD patients [20].

Vascular elasticity is easily and accurately detectable with advanced technologies. Elastic features of the aorta can be measured with invasive methods, or non-invasively with echocardiography or specific devices measuring pulse wave velocity. Quantitative measurement of the

Table II Comparison of aortic pressures and aortic elastic properties between patients with end-stage renal disease and healthy controls

Aortic parameters	ESRD (n = 96)	Controls ($n = 96$)	p value
Aortic systolic pressure (mmHg)	135.5 ± 21.9	118.2 ± 11.3	<0.001
Aortic diastolic pressure (mmHg)	84.1 ± 14.4	76.2 ± 8.6	<0.001
Aortic pulse pressure (mmHg)	51.4 ± 13.9	41.8 ± 8.1	<0.001
Aortic mean pressure (mmHg)	101.2 ± 16.1	90.2 ± 8.8	<0.001
Aortic fractional pulse pressure	0.51 ± 0.12	0.46 ± 0.09	0.005
Aortic pulsatility index	0.62 ± 0.18	0.55 ± 0.13	0.004
Aortic systolic diameter (mm)	33.1 ± 3.9	33.7 ± 3.8	0.426
Aortic diastolic diameter (mm)	31.1 ± 4.3	30.9 ± 3.8	0.646
Pulsatile aortic diameter change (mm)	2.07 ± 1.17	2.81 ± 0.98	<0.001
Aortic strain (%)	7.55 ± 5.27	9.97 ± 4.17	<0.001
Aortic distensibility (10^{-6} cm^2 dyn^{-1})	7.63 ± 5.75	8.41 ± 4.19	<0.001
Aortic stiffness index	3.24 ± 0.59	2.80 ± 0.34	<0.001
Aortic compliance (cm/mmHg)	0.043 ± 0.035	0.069 ± 0.028	<0.001

ESRD: end-stage renal disease

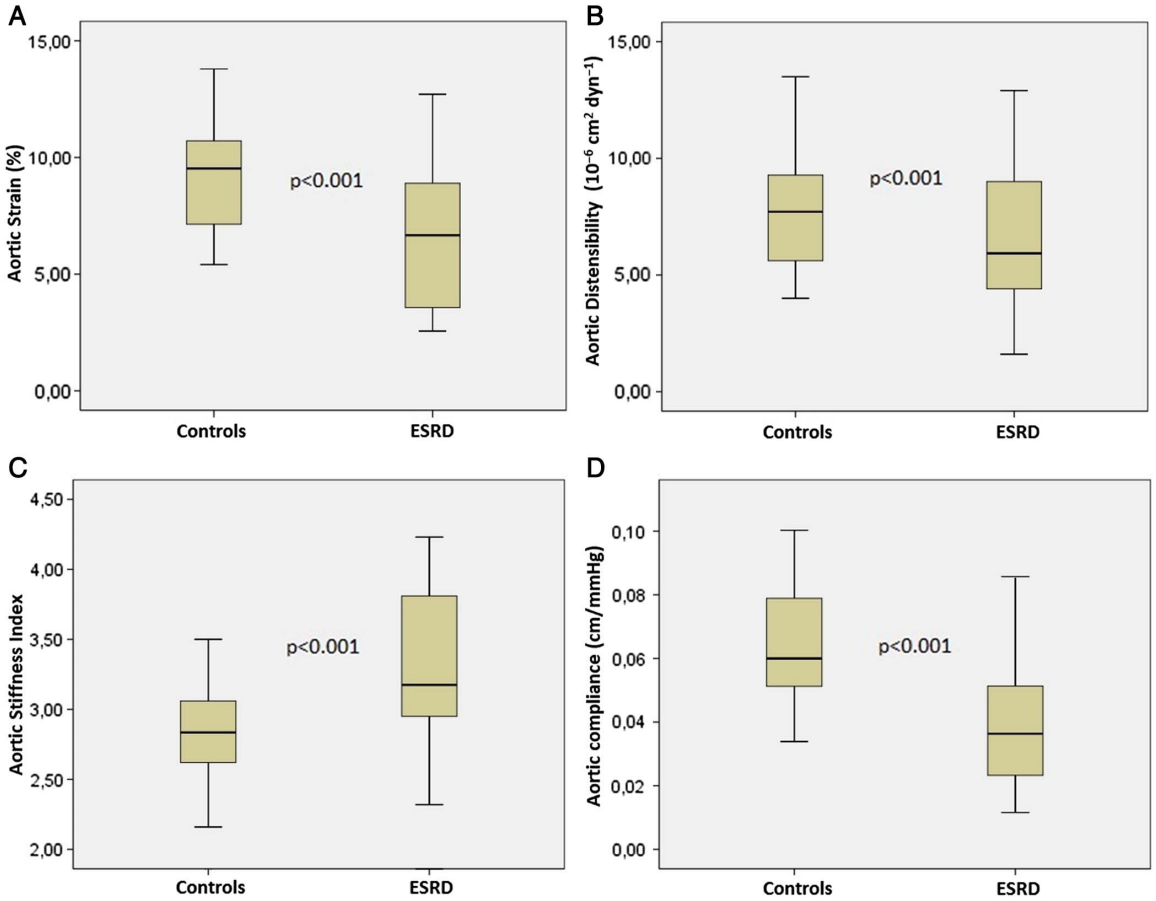

Fig. 1. Comparison of box-plot graphs of aortic strain (A), aortic distensibility (B), aortic stiffness index (C), and aortic compliance (D) between patients with end-stage renal disease (ESRD) and controls

elastic properties of the large arteries can be obtained by means of blood pressures and arterial diameters [21]. In this study, a non-invasive technique using blood pressures and aortic diameters measured by echocardiography was preferred.

Increased aortic stiffness and the presence of vascular calcification were typically observed in hypertensive patients with diabetes mellitus and have been associated with poor cardiovascular prognosis [22]. Therefore, we hypothesized that vascular calcification in patients with ESRD may also play a role in the development of aortic atherosclerosis and increased aortic stiffness. Consistent with the previous literature, we have found that the elastic properties of ascending aorta were decreased in patients with ESRD. Increased aortic stiffness may be caused by vascular calsifications, which are common pathological findings in patients with ESRD. In addition, despite exclusion of patients with known coronary artery disease, increased prevalence of diabetes mellitus and hypertension in ESRD group may bring together a high prevalence of subtle coronary artery disease in this group. Thus, increased atherosclerosis may directly affect the aortic wall and also the vasa vasorum, which originates from epicardial arteries and carries blood supply to the aortic wall.

Study limitations

The primary limitation was that this study was a non-randomized and single-center study with a relatively small number of patients. Second, pulse wave velocity, which is a new parameter of aortic elasticity, could not be measured in this study population due to technical deficiencies. Finally, coronary and aortic calcium scoring using computed tomography angiography would be useful in the evaluation of vascular calcifications in patients with ESRD.

Conclusions

The results demonstrated that a significant difference was present in terms of aortic blood pressures and echocardiographic parameters related to left ventricular hypertrophy and left atrial dilatation between patients with ESRD and controls. Furthermore, the elastic properties of ascending aorta were decreased, and aortic stiffness was increased in patients with ESRD as compared to healthy controls. Increased aortic stiffness may be partially responsible for the high cardiovascular risk in patients with ESRD.

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Authors' contribution: All the authors contributed in planning, conduct, and reporting of the work. They also had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: All authors declare no conflict of interest.

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