IntroductIon
Nitric oxide (NO), released from the endothelial cells, is a potent vasodilating agent with antiatherogenic properties. Several protective properties of NO in the vasculature are linked, among others, to the inhibition of platelet adhesion and aggregation, ability to lower the expression of endothelial surface adhesion molecules, lowering adhesion and infiltration of inflammatory cells into the endothelium, and reducing oxidative stress. NO may also contribute to regeneration of damaged endothelium, since it can mobilize the release of endothelial progenitor cells.

ABSTRACT

Introduction
Asymmetric dimethylarginin (ADMA) is an endogenous inhibitor of endothelial nitric oxide synthase, considered an effector of endothelial dysfunction. Among multiple diseases associated with elevated ADMA, chronic renal disease is often mentioned. ADMA is thought to be related to certain adverse cardiovascular effects of chronic uremia. The association between left ventricular (LV) structure and function and ADMA has been studied in numerous papers, but only few of them addressed this issue in end-stage renal disease (ESRD).

Objectives
The aim of the study was to analyze associations between serum ADMA (sADMA) levels and LV geometry and function in patients with ESRD treated with hemodialysis (HD).

Patients and Methods
The study group included 56 patients (31 women, 25 men) aged 59.0 ± 13.1 years, treated with HD for 70 ± 67 months. sADMA and biochemical parameters were measured and echocardiography was performed. sADMA levels were also measured in the control group of healthy individuals matched for age.

Results
Mean sADMA levels in patients were 2.39 ± 1.0 μmol/l and were significantly higher compared with controls (0.55 ± 0.12 μmol/l; P < 0.01). Based on echocardiography, patients were classified into the following groups: normal LV geometry (17.8%), concentric remodeling (8.9%), concentric hypertrophy (35.7%), excentric hypertrophy (37.5%), impaired systolic function (10.7%), and impaired diastolic function (71.4%) (1 patient could be in 1 or more groups). sADMA correlated with mean (r = 0.78; P < 0.05) and relative (r = 0.64; P < 0.05) LV wall thickness and with the LV mass index (r = 0.65; P < 0.05), but not with the indexes of systolic and diastolic function. sADMA was significantly higher in patients with excentric hypertrophy, concentric remodeling, and concentric hypertrophy compared with patients with normal LV geometry, and the highest was in patients with concentric hypertrophy.

Conclusions
Our study demonstrated an association between sADMA and disturbances in LV geometry in patients with ESRD treated with HD.
Asymmetric dimethylarginine (ADMA) is a strong endogenous inhibitor of the NO synthase (NOS); thus, it reduces NO availability and antagonizes most of the beneficial effects of this mediator. In the general population, an association has been observed between high serum ADMA (sADMA) and such diseases or disorders as ischemic heart disease, peripheral artery disease, arterial hypertension, insulin resistance, diabetes, smoking, postmenopausal period, high C-reactive protein, and dyslipidemia. ADMA occurs naturally in human metabolism and is efficiently eliminated with urine. In patients with chronic kidney disease (CKD), and especially in those with end-stage renal disease (ESRD), sADMA may be elevated up to 10-fold compared with healthy people.

ADMA is considered one of the important mediators of accelerated atherosclerosis in CKD, linking a decreasing renal function with progressing cardiovascular disease (a phenomenon that has recently been named cardio-renal syndrome type 4), given the fact that sADMA rises along with glomerular filtration rate (GFR) loss and intermittent hemodialysis (HD) does not eliminate it sufficiently from circulation. It has been demonstrated in a series of landmark studies by Zoccali et al. that ADMA is a strong and independent predictor of cardiovascular disease and mortality in patients with CKD.

One of the mechanisms that may explain the association between ADMA and cardiovascular disease in CKD is a plausible role of ADMA in the development of cardiac hypertrophy. NO and normal NOS activity are essential for the prevention of heart remodeling; therefore, decreased NO availability may lead to a loss of such protection. Several alternative mechanisms (except for NO deprivation) have also been proposed to explain the association between ADMA and cardiac hypertrophy. It has been demonstrated that ADMA can activate receptors for fibroblast growth factors in cardiomyocytes, thus leading to myocardial hypertrophy and fibrosis, or induce excessive local activation of the renin-angiotensin-aldosterone axis.

In the available literature, there are 2 studies that analyzed an association between sADMA and left ventricular (LV) structure and function. The Framingham Offspring Study investigators did not observe an association between ADMA levels and LV geometry or function as assessed with echocardiography in the general population. However, the above study did not include patients with serum creatinine exceeding 2 mg/dl. In another study, involving subjects with ESRD treated with HD, a correlation was found between ADMA levels, LV hypertrophy, and impaired systolic function.

Since the association between sADMA and LV geometry and function in patients with ESRD has not been well described, especially when diastolic LV function is concerned, we aimed to analyze possible correlations between sADMA and LV geometry and function in patients with ESRD treated with HD.

**Patients and Methods**

The study group included 56 patients (31 women and 25 men) aged between 18 and 79 years (mean ± standard deviation, 59.0 ±13.1). Patients were on maintenance dialysis due to ESRD for 70 ±67 months (range, 11–269 months). All patients were dialyzed 3 times a week using polysulphone membranes and bicarbonate-buffered dialysis fluid. Delivered dialysis dose could be considered adequate, with mean spKt/V of 1.38 ±0.38. The underlying causes of ESRD were as follows: diabetic nephropathy (n = 18), chronic primary glomerulonephritis (n = 11), interstitial nephritis (n = 7), polycystic kidney disease (n = 7), lupus nephritis (n = 2), reflux nephropathy (n = 1), renal tubular acidosis (n = 1), or unknown (n = 12). The control group included 25 healthy individuals aged 54.6 ±15.8 (range, 30–90 years; 11 men, 14 women).

The inclusion criteria were as follows: lack of permanent heart rhythm disorders, liver function tests not exceeding normal reference values by more than twice, absence of active inflammatory or infectious disease based on clinical evaluation and laboratory testing (subjects with hepatitis B surface antigen or anti-hepatitis C virus antibody positivity were eligible unless no clinical symptoms were present and respective polymerase chain reaction results were negative).

The study protocol was reviewed and approved by an independent ethics committee and the patients signed an informed consent prior to the first study procedure.

Fasting blood has been drawn to the sodium citrate or EDTA-containing tubes and centrifuged at the temperature of 4ºC with a speed of 1000 g for 15 to 30 minutes.

The obtained serum samples for ADMA were frozen and stored at −70ºC until processed. The remaining samples were assayed immediately. sADMA was assayed using the enzyme-linked immunosorbent assay (DLD Diagnostica GmbH, Hamburg, Germany). According to the manufacturer’s instructions, normal ADMA levels using this assay range from 0.4 and 0.75 μmol/l. The intra- and interassay variabilities for ADMA were from 3.2% to 5% and less than 5%, respectively.

The remaining laboratory parameters were assessed using standard techniques: peripheral blood morphology with Sysmex SF–3000 equipment (Roche Diagnostics, Poland); intact parathyroid hormone using ELECSYS 2010 (Roche Diagnostics); urea, creatinine, iron, total iron-binding capacity, calcium, phosphate, lipid profile, and aminotransferase activity – with HITACHI 912 (F. Hoffmann-LaRoche Ltd., Basel, Switzerland). Ferritin was measured with the Architect equipment (Abbott Labs, Abbott Park, Illinois, United States). Transferrin saturation was calculated as the ratio of serum iron concentration to total iron-binding capacity and expressed as percentage.
Single pool Kt/V to measure dialysis adequacy was calculated based on serum urea measured before and after the midweek dialysis and before the next dialysis session of the week. The Watson formula was used to calculate body fluid volume.

Echocardiography was performed using the VIVID 4 equipment (General Electric Healthcare, Waukesha, Wisconsin, United States) with the 2.5–3.5 MHz transducer and Doppler technique. Echocardiographic assessment was performed by an experienced cardiologist (A.G.) after a midweek HD. Interventricular septal diameter (IVSd) and posterior wall diastolic diameter (PWDd) were measured. The mean wall thickness (MWT) was calculated using the following formula: MWT (mm) = (IVS + PWT)/2, where IVS – interventricular septum and PWT – posterior wall thickness. The left ventricular end-diastolic diameter (LVEDd) was assessed in late diastolic phase. The relative wall thickness (RWT) was calculated using the formula: RWT = PWDd + IVSd/LVEDd, where IVSd = IVS thickness in diastole. The left ventricular mass (LVM) was measured using the Devereux and Reichek formula: LVM (g) = 1.04 × ([LVId + IVSd + PWT]³ – LVId³) – 13.6 g, where LVId = left ventricular internal diameter. The LVM index (LVMI) was calculated as the LVM to body surface area ratio and expressed in g/m².

Applying the Koren criteria, concentric hypertrophy was diagnosed in patients with increased LVMI and RWT of 0.45 cm or more, while eccentric hypertrophy – in those with increased LVMI and RWT of less than 0.45 cm. If RWT exceeded 0.45 but no signs of LV hypertrophy were observed, LV concentric remodeling was diagnosed. The ejection fraction (EF) was assessed according to Teichholz’s M mode assessment as the ratio between end-systolic and end-diastolic volume and expressed in percentage.

To estimate diastolic function of the left ventricle, mitral valve flow was assessed using the Doppler technique. The early (E) and late (A) diastolic mitral valve flow was measured and the E/A ratio calculated; E/A ratio of less than 1 may indicate impaired LV compliance in diastole.

Blood pressure (BP) was measured in a sitting position according to the Polish Society of Hypertension guidelines, which are in agreement with the European Society of Hypertension/European Society of Cardiology guidelines. BP was measured on the upper arm of the extremity without arterial occlusion, using the certified Omron M6 Comfort electronic sphygmomanometer (Omron Ltd., Kyoto, Japan). The mean arterial pressure (MAP) and pulse pressure (PP) were also calculated. Arterial hypertension was diagnosed as systolic BP (SBP) of 140 mmHg or higher and/or diastolic BP (DBP) of 90 mmHg or higher, or the use of BP-lowering drugs. The available medical documentation was carefully reviewed to record past cardiovascular and cerebrovascular events.

**Statistical analysis** The Shapiro-Wilk test for data distribution analysis was applied. For multiple group comparisons, the Kruskal-Wallis rank test was used. In the case of statistically significant differences, the Mann-Whitney test was applied for a post hoc analysis. The Spearman test was used to check correlations between the parameters. A multiple linear regression analysis using stepwise approach was conducted to identify independent variables that might affect the values of LVMI, MWT, and RWT. The P value of less than 0.05 was considered statistically significant. All calculations were performed using the STATISTICA for Windows 9.0 software (StatSoft, Inc, United States).

**RESULTS** The main comorbid conditions and detailed analysis of cardiovascular and cerebrovascular events are given in Table 1. Thirty-six patients had a history of at least 1 cardiovascular or cerebrovascular event (with 7.2% experiencing 3 or more events), 16 patients (28.6%) were on statins, and 13 (23%) on aspirin.

Mean SBP and DBP values were 146.2 ±24.6 and 80.9 ±13.2 mmHg, respectively, with PP of 65.4 ±18.4 and MAP of 102.8 ±15.5 mmHg. Forty-seven patients (84.1%) were considered hypertensive. The mean number of BP-lowering drugs per patient was 2.7 ±1.5. The results of biochemical parameters and a mean weekly dose of epeotin β are provided in Table 2.

The mean sADMA in patients was 2.39 ±1.0 μmol/l (median, 2.09; range, 0.78–4.78 μmol/l) and was significantly higher than in the control group (mean, 0.55 ±0.12 μmol/l; median, 0.57 μmol/l; range, 0.29–0.77 μmol/l; P < 0.01, Figure 1).

Detailed echocardiographic data are provided in Table 3. Based on the criteria listed in the section on patients and methods, we classified our patients according to echocardiographic findings into 6 groups: normal LV geometry (n = 10, 17.8%), concentric remodeling (n = 5, 8.9%), concentric hypertrophy (n = 20, 35.7%), eccentric hypertrophy (n = 21, 37.5%), impaired EF with EF below 45% (n = 6, 10.7%), and impaired diastolic function with E/A below 1 (n = 40, 71.4%).

**Table 1.** Comorbid conditions in the study group

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>diabetes</td>
<td>18 (32)</td>
</tr>
<tr>
<td>hypertension</td>
<td>47 (84.2)</td>
</tr>
<tr>
<td>cardiovascular/cerebrovascular event</td>
<td>36 (64.2)</td>
</tr>
<tr>
<td>myocardial infarction</td>
<td>7 (12.5)</td>
</tr>
<tr>
<td>revascularization (PTCA/CABG)</td>
<td>11 (19.6)</td>
</tr>
<tr>
<td>stroke/TIA</td>
<td>9 (16.0)</td>
</tr>
<tr>
<td>PAD/amputation</td>
<td>9 (16.0)</td>
</tr>
<tr>
<td>smoking</td>
<td>11 (7.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CABG – coronary artery bypass grafting, PAD – peripheral arterial disease, PTCA – percutaneous coronary angioplasty, TIA – transient ischemic attack
Relationship between serum asymmetric dimethylarginine and left ventricular structure...

sADMA correlated with MWT ($r = 0.78$, $P < 0.05$), RWT ($r = 0.64$, $P < 0.05$), and LVMI ($r = 0.65$, $P < 0.05$, FIGURES 2A, 2B, 2C). In contrast, no correlation was found between ADMA and the indexes of systolic and diastolic function. sADMA was significantly higher in patients with eccentric hypertrophy, concentric remodeling, and concentric hypertrophy compared with patients on HD with normal LV geometry, and the highest was in patients with concentric hypertrophy (FIGURE 3).

sADMA was also significantly higher in patients with hypertension compared with those with normal BP and in nonsmokers compared with smoking subjects (all differences, $P < 0.05$). Patients using 3 or more BP-lowering drugs had borderline significantly higher sADMA ($P = 0.08$) compared with those treated with 1 or 2 medications. No association was observed between ADMA and the type of BP-lowering drugs. Patients with diabetes had significantly higher sADMA levels ($P < 0.01$) than nondiabetics. Elevated sADMA was also observed in patients with a history of cardiovascular or cerebrovascular event; in addition, sADMA rose significantly with an increasing number of events (FIGURES 4A and 4B).

There were no correlations between sADMA and other parameters that might potentially affect the cardiovascular system of patients on maintenance dialysis including serum albumin, calcium and phosphate, intact parathyroid hormone, lipid profile, measures of iron stores, hemoglobin, and erythropoietin dose. sADMA did not correlate with age but was associated with dialysis vintage ($r = 0.53$, $P = 0.03$).

To identify independent variables that might affect the values of LVMI, MWT, and RWT, we applied the approach used previously by Zoccali et al.\textsuperscript{13} The results of multiple regression models...
The data demonstrate an independent association between ADMA and all 3 echocardiographic parameters.

**DISCUSSION**

Our study demonstrated that patients with ESRD had significantly higher sADMA levels compared with controls. An inverse association between declining kidney function as reflected by decreasing GFR and sADMA was shown by other investigators. Kielstein et al. observed that sADMA increased in the early stages of kidney disease, even if serum creatinine was within the normal range (i.e., below 1.3 mg/dl), independently of the type of underlying nephropathy. They concluded that elevated ADMA may be considered as a biomarker of early renal damage.

The same authors reported that in patients on HD, sADMA is 6-fold higher compared with healthy subjects (6.0 ±0.5 vs. 1.0 ±0.1 μmol/l; \( P < 0.05 \)). Significantly higher sADMA was also observed in ESRD patients treated with peritoneal dialysis (PD) compared with healthy controls, and within the PD group – in patients without residual renal function compared with those with preserved urine output. These data correspond to our results because in our study ADMA levels were 4-fold higher in HD patients compared with controls matched for age and sex (2.39 ±1.06 vs. 0.55 ±0.12 μmol/l; \( P < 0.01 \)).

The majority of our patients were hypertensive, which is in agreement with most epidemiological data showing that the prevalence of hypertension in CKD stage 5 patients reaches 85%–90%. An association between ADMA and BP is well established, and it appears to be present also in patients with CKD; elevated sADMA and NO deficiency translate directly into increased vascular stiffness.

Only few studies addressed the issue of a relationship between ADMA and arterial stiffness in patients on HD. Soveri et al. reported that lowering sADMA during HD can translate into decreasing augmentation index, a well-known measure of vascular stiffness. We demonstrated the relationship between sADMA and BP but not between sADMA and the class of BP-lowering drugs (probably due to a relatively small study group). In patients with essential hypertension and those with ESRD, an association has been reported between the use of the renin-angiotensin-aldosterone system blockade and decreasing ADMA levels.

ADMA did not correlate with erythropoietin dose or with peripheral blood cell counts. Several experimental data demonstrated that the development or worsening of hypertension associated with treatment with erythropoietin might potentially be related to disturbed NO metabolism pathways. Erythropoietin decreases endothelial NO synthesis and endotelial NOS expression in the experimental setting and may lead to a dose-dependent increase in sADMA when used in patients with CKD and renal anemia. In contrast to earlier reports, we failed to demonstrate any relationship between ADMA and lipid profile parameters or statin use.
both type 1 and type 2 diabetes; ADMA is also considered an important effector of renal damage in the development of diabetic nephropathy and predictor of cardiovascular events in early diabetes and advanced diabetic nephropathy.\cite{31}

Cardiovascular and cerebrovascular events were reported by 62% of the patients in our study, and these patients had higher sADMA levels, which increased with the increasing number of episodes. This finding is in agreement with other reports. In the general population (the Framingham Offspring Study with 3320 subjects), ADMA was related to mortality but not to cardiovascular events (myocardial infarction, coronary artery disease, congestive heart failure, stroke, or peripheral vascular disease).\cite{32} Both cardiovascular morbidity and mortality were associated with ADMA in ESRD patients treated with dialysis.\cite{9,12} Baseline sADMA was also higher in CKD patients not yet on dialysis who experienced a new cardiovascular event over the median follow-up period of 15 months, as compared with those without such events. Elevated sADMA appeared to be an independent risk factor for new cardiovascular events (with \( P < 0.001 \)).\cite{33} Thus, it might be hypothesized that possible prohypertrophic effect of ADMA is effective above a certain threshold level, found predominantly in CKD or ESRD patients, but not necessarily in the general population with normal or mildly elevated serum creatinine and relatively low prevalence of hypertension (as in the Framingham Offspring Study cohort).

Only 17.8% of our patients were considered normal in terms of the LV structure on echocardiography. In the remaining group, excentric hypertrophy was observed in 37.5% of the patients, concentric remodeling in 8.9%, and concentric hypertrophy in 35.7%. The majority of patients also suffered from functional LV disturbances, namely, impaired diastolic (71.4%) or systolic (10.7%) function. Surprisingly, patients who reported to be smokers had lower sADMA levels. In fact, the available literature provides conflicting results. Although smoking is considered the pivotal risk factor for the development of cardiovascular disease (and NO disturbances are important in such a relationship), there are reports showing both lower and higher levels of ADMA among smokers compared with non-smoking subjects.\cite{28-30}

sADMA was significantly higher in 32% of diabetic patients in our study. This finding has been uniformly confirmed in the studies on patients with

\begin{figure}
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\includegraphics[width=\textwidth]{figure3}
\caption{Serum ADMA in patients with normal LV geometry and 3 main LV disorders on echocardiography. Abbreviations: CH – concentric hypertrophy, CR – concentric remodeling, EH – excentric hypertrophy, N – normal LV, others – see Figures 1 and 2.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Serum ADMA and history of cardiovascular events; A – serum ADMA in patients with and without history of cardiovascular events; B – serum ADMA in relation to the number of cardiovascular events. Abbreviations: CV – cardiovascular, others – see Figure 1.}
\end{figure}
function. The rate of these abnormalities is in agreement with other studies. Excentric hypertrophy remains the most frequent LV abnormality observed in patients who start dialysis. In most of the echocardiographic studies in patients with ESRD, the parameters of diastolic LV function were not measured, while experimental data suggest extensive interstitial fibrosis developing in a uremic myocardium, which translates into significant disturbances in LV compliance. Our data confirm this observation, since more than 70% of the study patients were characterized with abnormal E/A ratio, a measure of diastolic LV performance.

Considering the relationship between ADMA and echocardiographic findings, we observed that sADMA was significantly and positively correlated with mean LV wall thickness, RVT, and LVMI. This may suggest the role of ADMA in the development of concentric LV hypertrophy. High flow velocity, early/late mitral inflow velocity, and isovolumetric relaxation time. A positive relationship between sADMA and LVMI was also reported in the group of CKD patients not yet on dialysis studied by Chinese researchers. These data in turn are in agreement with experimental and clinical studies that demonstrated the role of endothelial dysfunction, NO deficiency, and increased ADMA levels in the development of LV dysfunction and hypertrophy.

Our study has several limitations, the most important being the small sample group. Assuming that there were substantial differences in most of the analyzed biochemical and echocardiographic parameters between patients on HD and healthy controls, we limited the analysis in the control group exclusively to sADMA assessment.

In summary, our study is the second (after Zoccali et al.) to have demonstrated a significant association between sADMA and LV geometry disturbances in patients with ESRD on maintenance dialysis.

**REFERENCES**


Zależność między stężeniem asymetrycznej dimetyloargininy oraz strukturą i czynnością lewej komory serca u chorych ze schyłkową niewydolnością nerek leczonych hemodializami

Maria Napora¹, Anetta Graczykowska², Katarzyna Próchniewska², Zbigniew Zdrojewski³, Alicja Całka¹, Jerzy Górny², Tomasz Stompór¹

¹ Klinika Nefrologii, Hipertensjologii i Chorób Wewnętrznych, Uniwersytet Warmińsko-Mazurski, Olsztyn
² Oddział Kardiologiczny, Wojewódzki Szpital Specjalistyczny, Olsztyn
³ Katedra i Klinika Chorób Wewnętrznych, Chorób Tkanki Łącznej i Geriatrii, Gdański Uniwersytet Medyczny, Gdańsk

STRESZCZENIE

Asymetryczna dimetyloarginina (ADMA) jest endogennym inhibitorem śródbłonkowej syntazy tlenu azotu, uznawanym za czynnik patogenetyczny dysfunkcji śródbłonka. Wśród wielu patologii związanych ze zwiększeniem stężenia ADMA często wymienia się przewlekłą chorobę nerek. Uważa się, że ADMA jest jednym z czynników odpowiedzialnych za niekorzystny wpływ mocznicy na serce i naczynia. Zależność między sADMA a zaburzeniami struktury i czynności lewej komory (LK) serca była przedmiotem wielu prac, ale tylko nieliczne poświęcono badaniu tej zależności w schyłkowej niewydolności nerek (end-stage renal disease – ESRD).

CELE

Celem pracy była analiza zależności między ADMA w surowicy (serum ADMA – sADMA) a geometryą i czynnością LK serca u chorych z ESRD leczonych hemodializami (HD).

PACJENTY I METODY

Badanie przeprowadzono w grupie 56 chorych (31 kobiet, 25 mężczyzn) w wieku 59,0 ±13,1 roku, leczonych HD przez 70 ±67 miesięcy. Dokonywano pomiaru sADMA oraz profilu biochemicznego oraz wykonywano badanie echokardiograficzne. sADMA oceniano także w grupie kontrolnej osób zdrowych w porównywalnym wieku.

WYNIKI

Średnie sADMA w grupie HD wyniosło 2,39 ±1,0 μmol/l i było znamiennie większe niż w grupie kontrolnej (0,55 ±0,12 μmol/l; p <0,01). Na podstawie badania echokardiograficznego wyróżniono następujące kategorie chorych: z prawidłową geometrią LK (17,8%), z remodelingiem koncentrycznym (8,9%), z przerostem koncentrycznym (35,7%), z przerostem odśrodkowym (37,5%), z upośledzoną czynnością skurczową (10,7%) oraz z upośledzoną czynnością rozkurczową (71,4%) (1 chory mógł należeć do więcej niż 1 kategorii). sADMA korelowało ze średnią (r = 0,78; p <0,05) i względną (r  = 0,64; p <0,05) grubością LK oraz z upośledzoną czynnością rozkurczową (71,4%) (1 chory mógł należeć do więcej niż 1 kategorii). sADMA korelowało ze średnią (r = 0,78; p <0,05) i względną (r  = 0,64; p <0,05) grubością LK oraz wskaźnikiem masy LK (r = 0,65; p <0,05), nie korelowało jednak z parametrami czynności skurczowej i rozkurczowej. W porównaniu z chorymi z prawidłową geometrią LK sADMA było znamnie większe u chorych z przerostem odśrodkowym, remodeliowaniem koncentrycznym i przerostem koncentrycznym, a najwyższe u chorych z przerostem koncentrycznym. WNIOSKI

Badania wskazują na związek sADMA i nieprawidłowości w geometrii LK u chorych z ESRD leczonych HD.