Echocardiographic markers of left ventricular dysfunction among men with uncontrolled hypertension and stage 3 chronic kidney disease

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Background: Current guidelines for the management of arterial hypertension (AH) emphasize the importance of diagnosing subclinical organ damage, which determines cardiovascular prognosis. The aim of our study was to evaluate the prevalence of left ventricular hypertrophy (LVH), LV geometry patterns, and LV systolic/diastolic dysfunction among men with uncontrolled AH and chronic kidney disease (CKD) stages 3A and 3B.

Material/Methods: The study group included 256 men with essential AH. Glomerular filtration rate (eGFR) was calculated by the simplified MDRD equation. Left ventricular structure and function were assessed using echocardiography.

Results: Target blood pressure values were observed in 44 (17.2%) patients. In the studied group, eGFR <60 ml/min/1.73 m² was found in 67 (26.2%) subjects. Forty-nine (19.14%) patients were in stage 3A and 18 patients (7.03%) in stage 3B of CKD. We demonstrated that LVEDD, LA, RWT, and LVMI ECHO parameters were distinctly higher (p<0.05) in poorly controlled hypertensive patients in CKD stage 3B when compared with patients in CKD stage 3A. A significantly higher prevalence of LVH, including LV eccentric hypertrophy, was observed in stage 3B when compared to stage 3A of CKD (p<0.05). LVEF and E/A ratio decreased along with the decline of renal function (p<0.05).

Conclusions: Relationships between eGFR values and echocardiographic abnormalities of LV structure and function observed by us support the division of CKD stage 3 into 2 substages, 3A and 3B, as proposed by recently published guidelines. Intensification of therapeutic regimen in the CKD 3B subgroup is therefore crucial from both cardiological and nephrological perspectives.

Key words: chronic kidney disease • hypertension • left ventricular dysfunction

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Background

Arterial hypertension (AH) remains the most commonly diagnosed pathology of the cardiovascular (CV) system, especially in the people over age 50 [1]. Simultaneously, it is the most frequent modifiable risk factor for other diseases of the cardiovascular system (CVD). The prevalence of AH in the general population is estimated at between 20% and 50% and is increasing. The efficacy of its treatment is highly unsatisfactory [2,3].

Joint guidelines of the European Society of Hypertension/European Society of Cardiology (ESH/ESC) for the management of AH specified the target blood pressure (BP) values, the achievement of which reduces long-term CV risk [4].

These guidelines and ESH expert opinion also emphasize the importance of diagnosing subclinical organ damage (SOD) such as left ventricular hypertrophy (LVH) and chronic kidney disease (CKD), which constitute the next step in the development of CVD associated with AH [4,5]. Considering the possible reduction of SOD (and therefore CV risk) achieved through appropriate treatment, early diagnosis is key from the clinical point of view. Diagnostic procedures – electrocardiography, echocardiography (ECHO), and estimated glomerular filtration rate (eGFR) calculated using the MDRD (Modification of Diet in Renal Disease) formula – are recommended in the evaluation of hypertensive patients due to their simplicity, availability, and negligible costs [4,5]. Wherever possible, the same assessment should be used in diagnosing the damage of various organs such as heart, kidneys, and blood vessels, as multi-organ failure is associated with a significantly worse prognosis [6].

The role of ECHO in the diagnosis of hypertrophy and dysfunction of the left ventricle (LV) is well established [4,7,8]. Since 2002, National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) standards have been widely used to diagnose CKD [9]. According to them, the only criterion necessary for the diagnosis of CKD is a reduction of eGFR below 60 ml/min/1.73 m² or albumin-to-creatinine ratio (ACR) ≥30 mg/g for at least 3 months. Importantly, confirmation of kidney damage by other diagnostic methods is not required. In this situation “over-diagnosis” of CKD, which financially burdens the health system, is problematic. It may result from an uncritical, wide application of the formulas for the estimation of GFR (especially the MDRD formula) in all age groups and skipping such factors as the other markers of kidney damage, “chronicity”, and overall clinical picture in the diagnosis of CKD [10,11]. According to Levey et al., the CKD definition and classification used in everyday practice should primarily reflect the clinical state and prognosis of the patient [12].

Recent data indicate that a significant increase in risk of mortality and CV events is observed when eGFR is below 45 ml/min/1.73 m² [13–16]. Accepting this as a basis and taking into consideration the observations of the “physiological” decline of eGFR associated with age and sex, the NICE Institute (National Institute for Health and Clinical Excellence, UK) creating guidelines for physicians practicing in the United Kingdom has proposed a subdivision of stage 3 of CKD into two stages: 3A and 3B and to add suffix (p) to denote the presence of proteinuria. The cut-off point used for this division was the value of eGFR 45 ml/min/1.73 m². According to this, stage 3A includes the values of eGFR 45–59 ml/min/1.73 m² and 3B includes values: 30–44 ml/min/1.73 m². This new classification of CKD has been proposed to obtain a more accurate assessment of overall and CV risk in the hypertensive population and, consequently, the choice of adequate renoprotective strategy [17,18].

A collaborative meta-analysis initiated in 2009 by the Kidney Disease: Improving Global Outcomes (KDIGO), which included 1 555 332 participants from general, high-risk, and kidney disease populations examined the relationship of eGFR and albuminuria to all-cause and CV mortality and kidney outcomes. Analysis of the obtained data confirmed that in the range of eGFR 30–59 ml/min/1.73 m² there was a steep rise in risk with lower eGFR, consistent with NICE suggestions to subdivide stage 3 at eGFR of 45 ml/min/1.73 m². Revised CKD classification proposed by KDIGO also involves addition of 3 albuminuria ranges at all GFR stages [12].

The aim of our study was to evaluate the prevalence of LVH, left ventricular geometry patterns, and LV systolic/diastolic dysfunction among men with poorly controlled hypertension and CKD stage 3 according to NICE guidelines.

Material and Methods

Patients

The study was approved by the Ethics Committee of Warmia and Mazury Medical Chamber, Olsztyn, Poland. The study group included 256 men (aged 27–90 years) with pharmacologically treated essential AH, living in the province of Warmia and Mazury, and remaining under medical supervision in the outpatient cardiology practice. The exclusion criteria were: eGFR below 30 ml/min/1.73 m², established atrial fibrillation, prior myocardial infarction, history of renal replacement therapy, disabling disease, malignancy, and secondary AH. Study participants underwent a detailed review of their medical history and physical examination based on a prepared questionnaire. Blood pressure (BP) was measured in a sitting position according to the ESH guidelines (measurements were made after a 5-minute rest in a sitting position with a certified mercury sphygmomanometer; an average of 3 measurements made at an interval of at least 2 minutes was used in the analysis)
[19]. The mean arterial pressure (MAP) was calculated using the formula – MAP = DBP+1/3×(SBP-DBP), where SBP is systolic and DBP diastolic BP. The pulse pressure (PP) was the difference between SBP and DBP. Target BP values were established separately for patients without known CVD or diabetes (<140/90 mmHg) and for subjects with diagnosed CVD or diabetes (<130/80 mmHg). Body mass index (BMI) was calculated using the formula: BMI = weight [kg]/height [m]^2 [4]. The available medical documentation was carefully reviewed to record past CV events (myocardial infarction, stroke), diabetes history, and current antihypertensive treatment.

**Biochemical measurements**

Laboratory measurements included determination of glucose, total cholesterol, HDL cholesterol, triglycerides, uric acid, and creatinine serum concentrations (Integra 400, Roche Diagnostics). LDL cholesterol concentration was calculated according to the Friedewald’s formula. eGFR was calculated by the simplified MDRD equation [4,9]. Chronic kidney disease (CKD) was diagnosed in subjects with eGFR <60 ml/min/1.73 m^2. According to the NKF-KDOQI (2002) classification and NICE (2008) guidelines, subjects were qualified for 1 of 3 groups: 2 – eGFR ≥60 ml/min/1.73 m^2, 3A – eGFR 45–59 ml/min/1.73 m^2, and 3B – eGFR 30–44 ml/min/1.73 m^2 [4,17,18]. Urinary albumin/creatinine ratio (ACR) was not a subject of our study.

**Echocardiography**

Echocardiography was performed using the General Electric Vivid 4 system (General Electric Healthcare, Waukesha, WI) with the 2.5–3.5 MHz transducer and Doppler technique. Images were taken in left decubitus position. M-mode echocardiography was performed to evaluate left ventricular end-diastolic diameter (LVEDD), interventricular septum thickness (IVST), posterior wall thickness (PWT), and left atrium diameter (LA). The left ventricular mass (LVM) was measured according to the American Society of Echocardiography. The obtained values of LVM were indexed to body surface area and are presented as left ventricle mass index (LVMI) [7,20]. According to ESH/ESC guidelines, LVH was diagnosed when LVMI was ≥125 g/m^2 [4]. On the basis of simultaneous evaluation of relative wall thickness (RWT = PWT+IVST/LVEDD) and LVMI, the following patterns of LVH were obtained: concentric LVH (LVMI ≥125 g/m^2 and RWT of 0.45 and more), eccentric LVH (LVMI ≥125 g/m^2 and RWT of less than 0.45), concentric remodeling of LV (if RWT exceeded 0.45 and no signs of LVH were noted) [21]. Left ventricular ejection fraction (LVEF) was assessed using Simpson’s rule [22]. Diastolic function was evaluated using mitral inflow profile parameters (E and A waves, E/A ratio) with pulsed-wave Doppler echocardiography. E/A ratios of less than 1 indicate impaired LV compliance in diastole [23].

| Parameter                        | All N=256 |
|----------------------------------|-----------|
| Duration of hypertensive treatment [years] | 10.7±6.7  |
| Age [years]                      | 64.9±12.1 |
| SBP [mmHg]                       | 147.1±22.5|
| DBP [mmHg]                       | 88.8±12.9 |
| PP [mmHg]                        | 59.8±17.0 |
| MAP [mmHg]                       | 109.5±14.2|
| BMI [kg/m²]                      | 29.5±4.8  |
| Family history of CVD, n (%)     | 233 (91.0)|
| Smoking, n (%)                   | 143 (55.9)|
| Ischaemic heart disease, n (%)   | 198 (77.3)|
| Diabetes, n (%)                  | 74 (28.9) |
| Lipid metabolism abnormalities in anamnesis, n (%) | 159 (62.1) |

**Antihypertensive medication**

- Diuretics, n (%) | 123 (48.0) |
- Beta blockers, n (%) | 179 (69.9) |
- ACEI, n (%) | 184 (71.9) |
- Ca blockers, n (%) | 70 (27.3) |
- Alfa blockers, n (%) | 52 (20.3) |
- ARB, n (%) | 13 (5.1) |

Values are mean ±SD. SBP – systolic blood pressure; DBP – diastolic blood pressure; PP – pulse pressure; MAP – mean arterial pressure; BMI – body mass index; CVD – cardiovascular disease; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin-receptor blocker.

**Statistical analysis**

All quantitative data are presented as mean ± standard deviation (SD). Comparisons between groups were conducted using the t test or Cochran-Cox test for quantitative variables and the chi-squared test for categorical variables. A value of p<0.05 was recognized as statistically significant. The statistical analyses were performed using the Statistica for Windows 6.0 PL software package (StatSoft Inc., USA).

**Results**

The main clinical characteristics of the study group are reported in Table 1.
The mean age in the studied population was 64.9±12.1 years, with a predominance of men aged 56–65 (30.1%) and 66–75 (27.7%) years. Mean SBP and DBP values were 147.1±22.5 mmHg and 88.8±12.9 mmHg, respectively, with PP of 59.8±17.0 and MAP of 109.5±14.2 mmHg. Two hundred fifteen patients (84%) were overweight and 74 (28.9%) had diabetes. During medical examination, 233 (91%) men reported family history of cardiovascular disease and 198 (77.3%) had ischemic heart disease.

The results of biochemical parameters are presented in Table 2.

In the whole studied population, the eGFR <60 ml/min/1.73 m² was found in 67 patients (26.2%). Forty-nine (19.14%) patients were in stage 3A and 18 patients (7.03%) were in stage 3B of CKD.

Detailed echocardiographic data of the studied population is presented in Table 3.

Based on criteria listed in the section on methods, we divided the studied population into 4 groups of LV geometry: normal LV geometry (n=112; 44.1%), concentric remodeling (n=35; 13.7%), eccentric hypertrophy (n=66; 25.4%), and concentric hypertrophy (n=43; 16.8%).

Subjects had highly unsatisfactory control of blood pressure. Target blood pressure values were observed in 44/256 patients (17.2%). Poor control of hypertension occurred mainly in men with coronary heart disease and/or type 2 diabetes. In this group, adequate blood pressure values were noted only in 29/212 subjects (13.3%). Ineffective control of hypertension was found significantly more often in men with ischemic heart disease.

Among ineffectively treated hypertensive patients, ECHO revealed distinctly larger dimensions of left heart cavities, thicker LV walls, increased LVM and LVMI, and lower indicators of systolic and diastolic LV function (LVEF and E/A ratio). This group much more often (p<0.01) met the criteria for LVH – 49.5% vs. 6.8%. Among men with poor hypertension control,
mean values of eGFR were lower (p<0.01) and eGFR value below 60 ml/min/1.73 m² was recognized significantly more often (p=0.01) (Table 4).

We investigated patients with poor control of hypertension according to their stage of CKD and found increasingly higher diameter and thickness of LV, LA, and LVMI along with the decreasing renal function (Table 5). Statistical analysis demonstrated that ECHO parameters such as LVEDD, LA, RWT, and LVMI were significantly higher (p<0.05) in patients in stage 3B when compared with patients in stage 3A of CKD. Similarly, a decidedly higher prevalence of LVH, including left ventricular eccentric hypertrophy, was recognized significantly more in patients in stage 3B of CKD (Table 5).

Table 4. Analysis of the effectiveness of antihypertensive therapy according to the studied echocardiographic parameters and eGFR values.

| Parameter   | Effective n=44 | Ineffective n=212 | p     |
|-------------|----------------|-------------------|-------|
| LVEDD [cm]  | 5.11±0.36      | 5.45±0.56         | <0.01 |
| LA [cm]     | 3.70±0.43      | 4.03±0.52         | <0.01 |
| IVS [cm]    | 1.04±0.15      | 1.16±0.16         | <0.01 |
| LVPW [cm]   | 1.01±0.11      | 1.10±0.13         | <0.01 |
| LVEF [%]    | 0.42±0.3       | 0.55±0.4          | <0.01 |
| E/A         | 0.99±0.11      | 0.95±0.19         | 0.05  |
| LVM [g]     | 197.9±49.8     | 248.5±53.4        | <0.01 |
| LVMI [g/m²] | 99.1±27.0      | 124.4±27.8        | <0.01 |
| LVH (LVMI ≥125 g/m²), n (%)| 3/44 (6.8) | 105/212 (49.5) | <0.01 |
| eGFR [ml/min/1.73 m²], n (%)| 80.6±16.8 | 70.0±17.6 | <0.01 |
| eGFR <60 [ml/min/1.73 m²], n (%)| 5/44 (11.4) | 62/212 (29.3) | 0.01 |

Values are mean ±SD. For abbreviations see Tables 2 and 3.

Table 5. Echocardiographic data of poor controlled hypertensive in patients with different stages of chronic kidney disease.

| Parameter   | -60 n=150 | (45–59) n=46 | (30–44) n=16 | Significant differences between groups (p<0.05) |
|-------------|-----------|--------------|--------------|-----------------------------------------------|
| LVEDD [cm]  | 5.39±0.50 | 5.44±0.60    | 6.03±0.74    | 2-3B, 3A-3B                                  |
| LA [cm]     | 3.99±0.49 | 4.01±0.53    | 4.52±0.57    | 2-3B, 3A-3B                                  |
| LVEF [%]    | 57.1±8.0  | 53.6±11.5    | 47.3±11.7    | 2-3A, 2-3B, 3A-3B                            |
| E/A ratio   | 1.02±0.15 | 0.84±0.18    | 0.65±0.13    | 2-3A, 2-3B, 3A-3B                            |
| LVM [g]     | 243.5±53.8| 254.7±51.7   | 277.3±44.6   | 2-3B                                         |
| LVMI [g/m²] | 121.3±27.7| 127.7±26.3   | 143.7±25.3   | 2-3B, 3A-3B                                  |
| RWT         | 0.42±0.06 | 0.43±0.07    | 0.37±0.07    | 2-3B, 3A-3B                                  |
| LVH (LVMI ≥125), n (%)| 65/150 (43.3) | 27/46 (58.7) | 13/16 (81.3) | 2-3B, 3A-3B                                  |
| LV eccentric hypertrophy, n (%)| 36/150 (24.0) | 16/46 (34.8) | 11/16 (68.8) | 2-3B, 3A-3B                                  |

Values are mean ±SD. LVH – left ventricular hypertrophy. For other abbreviations see Table 3.
eccentric hypertrophy, was observed among patients in stage 3B when compared with patients in stage 3A of CKD (p<0.05). In relation to systolic and diastolic function, LVEF and E/A ratio both decreased along with the decline of renal function (p<0.05). There were no statistically significant differences between values of IVS and LVPW and the incidence of patterns of LVH (e.g., normal geometry, concentric remodeling, and concentric hypertrophy) between different stages of CKD.

**Discussion**

The studied group of hypertensive men was characterized by high cardiovascular risk due to high incidence of coronary heart disease, classical CVD risk factors, and above all, unsatisfactory BP control. Our results confirm observations of other authors on inadequate hypertension control in the European population. In a German epidemiological study published in 1999, satisfactory BP control was found in 30% of patients [24]. Banegas et al. in 1998 demonstrated that only 15% of hypertensive patients from Spain achieved target BP values [25]. In Polish studies conducted by Zdrojewski et al. in 2001, adequate control of AH was found only in 12% of patients [26]. The BP-CARE study (Blood Pressure Control and Cardiovascular Risk Rate Profile) published in 2011 and involving nearly 8000 patients from nine countries in Central and Eastern Europe (except Poland), showed that despite the wide use of 2 or more antihypertensive drugs, adequate BP control was achieved in only 27% of patients [27].

The ESH/ESC guidelines and ESH expert opinion emphasize the importance of diagnosing subclinical organ damage, such as LVH and CKD, associated with increased cardiovascular risk among hypertensive men [4,5]. In our study, according to LVMI value and the eGFR value <60 ml/min/1.73 m², cases of LVH were found in 42.2% and 26.2%, respectively, of all patients. It should be noted that, in agreement with the epidemiological data, these complications occurred decidedly more frequently among subjects with inadequately treated hypertension. Cea-Calvo et al., in a study of nearly 2500 patients with hypertension, found that nearly 23% of patients met the criteria for LVH and 45% for CKD, and that these complications related mainly to the unsuccessfully-treated group [28]. Mancia et al., in the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni) involving approximately 2000 hypertensive patients, found that ineffective treatment is associated with significantly higher incidence of echocardiographically diagnosed LVH [29]. Leoncini et al., in a study of 3500 patients with hypertension and diabetes, recognized CKD in 42%, mainly in the subgroup with uncontrolled AH [30].

Co-existing kidney damage and left ventricular hypertrophy are associated with worse prognosis in patients with AH. According to Leoncini et al., manifestation of LVH in patients with moderate decrease in GFR (<60 ml/min/1.73 m²) in the course of hypertension may be responsible for the increased cardiovascular risk in this group of patients [31]. The prevalence of this complication in the early stages of CKD (defined according to KDOQI as eGFR 30–59 ml/min/1.73 m³) is estimated at from 34% to 78% [32–34]. Less is known about the occurrence of LVH and other indices of LV function in CKD stages 3A (eGFR 45–59 ml/min/1.73 m³) and 3B (eGFR 30–44 ml/min/1.73 m³) according to NICE guidelines [17,18].

In our study, left LV hypertrophy and other echocardiographic markers of LV dysfunction occurred distinctly more often in the group of patients with ineffectively treated AH and with eGFR values below 60 ml/min/1.73 m³, which confirms observations of other authors [32–35]. More importantly, we observed a significant difference in the incidence of studied parameters between analyzed CKD stages 3A and 3B. This concerns both the higher incidence of LVH (as well as higher values of parameters such as LVMI) and the larger diameters of the left heart chambers (LV and LA) noted in CKD stage 3B. This finding is important because the presence of LVH and increased dimensions of left heart chambers have become well-established predictors of poor CV prognosis [36–38]. Considering the types of LV geometry, the eccentric form of LVH was found significantly more often among men in CKD stage 3B. Our results confirm the high prevalence of this pattern of LVH in hypertensive patients with moderate reduction of kidney function. In the study of Eckardt et al., involving 450 CKD patients, eccentric LVH was most common and associated with poor CV outcomes among patients with CKD stages 3 to 4 [39].

Another finding of our study derives from the analysis of E/A ratio, which was used to evaluate LV diastolic function. E/A ratio values were found to be lower along with decrease of renal function. We observed significantly lower values of this parameter among men in stage 3B when compared to those in stage 3A of CKD. This is important because impaired LV diastolic function may be connected with development of heart failure and related to high CV risk in this population [40].

Among men with poor AH control and early CKD stages, we observed LV systolic dysfunction features assessed by LVF; in stage 3A, mean LVEF was 53.6±11.5% and in stage 3B it was 47.3±11.7% (p<0.05). Decrease of LVEF below 50% is a predictor of CV events and death among patients with ischemic heart disease in the general population, as well as among patients on chronic dialysis [41]. Wu et al. showed that among patients with angiographically confirmed ischemic heart disease and CKD, lower eGFR values were associated with lower values of LVEF. They also demonstrated that reduced LVEF was an independent prognostic indicator of mortality from all causes in this group of patients [42].
Parker et al. noted that despite the increased use of chronic hemodialysis for treatment of end-stage renal disease (ESRD), overall annual mortality in this group of patients has declined by only 1% per decade in the United States and average hospitalization rate has remained steady [43]. Locatelli and Cannaud reached a similar conclusion analyzing a European population [44]. This stagnation may be the result of inadequate prior and current guidelines for dialysis therapy. In this situation new recommendations for ESRD treatment need to be pursued. According to Parker et al., focus on prevention or reversal of the increase in the LV mass (“mind the left ventricle”) is one of them and should replace the excessive focus on atherosclerotic coronary artery disease in the hierarchy of treatable CV morbidities (as emphasized by current clinical guidelines) among CKD patients. This is because LV hypertrophy is closely related to myocardial fibrosis, systolic and diastolic dysfunctions, and markedly increased risk of arrhythmogenic sudden cardiac death or congestive heart failure, which in turn translates into fatal prognosis in this population [36–38,43].

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Conclusions

Relationships between eGFR values and echocardiographic abnormalities of LV structure and function observed by us support the decision of CKD stage 3 into 3A and 3B subgroups, as proposed by recently published KDIGO guidelines [45]. Unfavorable LV echocardiographic characteristics of subjects classified by us as stage 3B confirm a higher cardiovascular risk in this group of men. Intensification of therapeutic regimen in this group of patients (as proposed by NICE and KDIGO) is therefore crucial from both cardiological and nephrological perspectives.

The most important limitation of our study is the small number of subjects. Therefore, well-designed studies with larger sample sizes are needed to confirm our observations.
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