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Left ventricular diastolic dysfunction in a general population-based sample without previous cardiac disease: concomitant physical and laboratory variables

Dysfunkcja rozkurczowa lewej komory w populacji ogólnej bez wcześniejszej choroby serca — współistniejące czynniki fizyczne i laboratoryjne

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Abstract

Introduction. Left ventricular diastolic dysfunction (LVDD) is described as impaired left ventricular (LV) relaxation and reduced chamber compliance. Misleading data on the prevalence of LVDD are available in the literature due to various definitions. This study aimed to assess the frequency of LVDD in a population without severe cardiovascular disease (CVD), as well as to identify factors associated with it.

Material and methods. Overall, 648 individuals without severe CVD were included. LVDD was assessed using the last 2016 guidelines ($LVDD_{2016}$) together with the previous recommendations from 1998 ($LVDD_{1998}$).

Results. In total, 35 participants (5.4%) met the $LVDD_{2016}$ criteria, and 29 people (4.5%) fulfilled only the $LVDD_{1998}$ criteria. The strongest factors independently associated with $LVDD_{2016}$ were body mass index (BMI), high-sensitivity C-reactive protein, high-sensitivity troponin T, ejection fraction and circumference of neck and waist. $LVDD_{2016}$ presents a significant association with the anthropometric measures (BMI, neck and waist circumference), LV function and overload as well as the inflammatory parameter.

Conclusions. In the population without overt CVD the frequency of LVDD as defined by the latest 2016 guidelines is 5.4%. It was associated with inflammatory, cardiac damage and anthropometric parameters.

Key words: left ventricular diastolic dysfunction, echocardiography, population study, risk factors

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Introduction

Left ventricular diastolic dysfunction (LVDD) is understood as impaired left ventricular (LV) relaxation with or without reduced restoring forces and reduced chamber compliance. This is the result of the increased wall stiffness that causes the inability of the LV to fill adequately under anomalous or normal atrial pressure both at rest or during exercise [1]. LVDD is believed to be one of the key determinants of cardiac function and can occur in asymptomatic patients. There is strong evidence for a pathophysiological association between LVDD and symptoms in many heart failure (HF) patients, both with preserved and reduced ejection fraction (EF) [2, 3]. Scientists are increasingly focusing on LVDD as an independent predictor of cardiovascular events in general population studies and are constantly looking for factors associated with it [4–6].

A common problem for a clinician is the plethora of various definitions of LVDD. Researchers sometimes use individual echocardiographic parameters, confusingly calling them LVDD. The latest guidelines encourage the assessment of LVDD based on a full echocardiographic algorithm, which is the result of many years of research and observation. Unfortunately, few publications base the assessment of LVDD on the full algorithm. Therefore, it was aimed to assess the frequency of LVDD in the general population as well as to identify factors associated with it. Additionally, the differences between the LVDD assessments were also examined according to different guidelines.

Material and methods

Among the people registered in the city of Bialystok, a sample of the population was selected, proportionally in terms of age and sex to the distribution of the population of Białystok residents. The described group aged 20–80 years was studied in the period 2018–2020. Overall, 1,847 residents, were invited to participate in the study, 713 accepted the invitation and were examined. For this study, 65 participants were excluded for the following reasons: a history of myocardial infarction (n = 15), atrial fibrillation (n = 18), previous stroke (n = 10), chronic coronary heart disease other than myocardial infarction (n = 9), peripheral arterial disease (n = 3), reduced EF below 45% in the current echocardiography (n = 6), the lack of complete echocardiography (n = 4). As a result, 648 people were included in the study group.

The information about the participants' medical histories and demographic data was collected with the use of an extensive questionnaire at the time of the study entry. All subjects underwent a physical examination and blood sampling for laboratory evaluation. Peripheral intravenous blood samples were drawn after an overnight fast. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Waist-to hip ratio (WHR) was obtained by dividing the waist circumference by the hip circumference.

Transthoracic echocardiography including B-mode, pulsed wave Doppler and tissue Doppler was performed using ultrasound Vivid 9 (GE Healthcare, USA). Measurements of the size of the heart cavities, left atrial (LA) volume and left ventricular ejectiona fraction (LVEF) using the biplane method were made according to the joint American and European guidelines [7]. The LA volume index (LAVI) was calculated by the formula LA volume/body surface area (BSA). The Devereux Formula was used to calculate LV mass (LVM) which was consequently applied to calculate LV mass index (LVMI) (LVMI = LVM/BSA) [8].

For this study, LVDD has been defined using two different definitions (Table 1). $LVDD_{2016}$ [1] was based on the current European Association of Cardiovascular Imaging/American Society of Echocardiography (EACVI/ASE) 2016 recommendations (Figure 1) and was determined as previously described [4]. Overall, 35 participants (5.4%) were included in this group from study sample. In this study, the categories of diastolic dysfunction: "indeterminate" and "abnormal" were fused into one ($LVDD_{2016}$). $LVDD_{1998}$ group contains participants who were not in $LVDD_{2016}$ but presented diastolic abnormalities as proposed by the European Study Group on Diastolic Heart Failure in 1998 [9]. In the studied population, 29 people (4.5%) fulfilled these criteria.

Body composition was assessed by dual-energy X-ray absorptiometry (DEXA) (GE Healthcare, USA). Fat mass index (FMI) and lean mass index (LMI) was calculated as fat and lean mass in kilograms divided by height in meters squared. The anthropometric measurements such as the circumference of the neck, waist and hips were measured with the tape in a standing position. Artery stiffness parameters, i.e., brachial-ankle pulse wave velocity (PWV_{ba}) and central pressure (CP) were measured using the oscillometric method (Vascular Explorer, Germany). Blood pressure (BP) was measured twice using the oscillometric method (Omron Healthcare Co. Ltd.) at 5-minute intervals. Hypertension was defined as systolic BP > 140 mm Hg, or diastolic BP > 90 mm Hg, or a history of hypertension, or use of antihypertensive agents. The study population was assessed for cardiovascular (CV) risk classes and categorized according to the latest European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommendations [10]. The concentrations of cortisol, interleukin 6 (IL-6), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT) were determined by the electrochemiluminescence method on the Cobas E411 (Roche). The lipid profile glucose concentration and high-sensitivity C-reactive protein (hs-CRP) were determined on the Cobas C111.

Ethical approval for this study was provided by the Ethics Committee of the Medical University of Bialystok (Poland)

Table 1. Algorithm evaluation of left ventricular diastolic dysfunction (LVDD) (based on [1, 4, 9])

$LVDD_{2016}$	Normal EF (≥ 50%)	1. Average E/e' > 14 2. Septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s 3. TR velocity max > 2.8 m/s 4. LAVI > 34 mL/m^2	1st criteria fulfilled	Normal LVDD
			2nd criteria fulfilled	Indeterminate LVDD
			3rd or 4th criteria fulfilled	Abnormal LVDD
	Depressed EF (< 50%)	E/A ≤ 0.8 + E ≤ 50 cm/s		Grade I LVDD
		E/A ≤ 0.8 + E > 50 cm/s or 0.8 < E/A < 2	When possible assessment of 3 criteria: 1. Average E/e' > 14 2. TR velocity > 2.8 m/s 3. LAVI > 34 mL/m^2	2 of 3 or 3 of 3 Negative
			When only 2 criteria are available: 2 negative	Indeterminate LVDD
			When only 2 criteria are available: 1 positive and 1 negative	Indeterminate LVDD
			When only 2 criteria are available: 1 negative	Grade II LVDD
			2 of 3 or 3 of 3 Positive	Grade III LVDD
		E/A ≥ 2		
$LVDD_{1998}$	EF ≥ 45%	$IVRT_{<30y>}$92 ms, $IVRT_{30–50y>}$100 ms, $IVRT_{>50y>}$105 ms and/or $E/A_{<50y<}$1.0 and $DT_{<50y>}$220 ms, $E/A_{>50y<}$0.5 and $DT_{>50y>}$280 ms		

A — peak late diastolic velocity; DT — deceleration time; e' — early diastolic mitral annular tissue velocity; E — peak early diastolic velocity; EF — ejection fraction; IVRT — isovolumetric relaxation time; LAVI — left atrial volume index; TR — tricuspid regurgitation

on 31 March 2016 (approval number: R-I-002/108/2016). All participants provided written informed consent.

Depending on the normality of the distribution, descriptive statistics for quantitative variables were presented as mean ± standard deviation or median [with interquartile range (IQR) 1st quartile–3rd quartile], while as counts and frequencies for qualitative variables. Comparisons of variables between subgroups were conducted using the Kruskal-Wallis or Fisher's tests with a Tukey's Honest Significant Difference test as a post-hoc test. Associations between $LVDD_{1998}$, $LVDD_{2016}$ and other clinical and biochemical variables were analysed using the unadjusted and multiple logistic regression models. Logistic regression models were presented using odds ratio and 95% confidence intervals. Statistical hypotheses were verified at the 0.05 significance level. The IBM SPSS Statistics 26.0 statistical software (Armonk, USA) was used for all calculations.

Results

Table 2 provides a comparison of the characteristics of groups with $LVDD_{1998}$, $LVDD_{2016}$ and without LVDD. The individuals with $LVDD_{2016}$ were older, most frequently reported dyspnoea ($p = 0.008$) and fatigue during exercise ($p < 0.001$). The group with $LVDD_{2016}$ differed significantly from the group without LVDD in terms of BMI ($p = 0.001$), neck ($p < 0.001$), waist ($p < 0.001$) and hips ($p = 0.002$) circumference. Also, the differences between these groups were observed in the measurements of pressures: systolic blood pressure (BPs) ($p = 0.004$), diastolic blood pressure (BPd) ($p = 0.001$), systolic central pressure (CPs) ($p = 0.002$) and PWV_{ba} ($p = 0.007$). In laboratory tests, the highest concentration of fasting and 120 minutes glucose in oral glucose tolerance test (OGTT) ($p = 0.013$, $p = 0.016$, respectively), HbA1c (hemoglobin A1c) ($p = 0.001$), hs-TnT ($p = 0.010$) were in the $LVDD_{2016}$ group. $LVDD_{1998}$ population was similar to the group without LVDD.

In Model 1, multivariable logistic regression analysis (Table 3), $LVDD_{2016}$ was associated with higher BPs, BPd and CPs. Moreover, among the laboratory variables, hs-TnT, cortisol and carbohydrate metabolism indicators (fasting glucose, HbA1c) were significantly associated with $LVDD_{2016}$. In Model 3, a significant relationship between $LVDD_{2016}$ and BPd, hs-CRP, hs-TnT and cortisol was confirmed. An analogous comparison of factors associated with the occurrence of LVDD according to the 1998 guidelines was reported in the Table 4. In the following regression models, $LVDD_{1998}$ was found to be related only to the CP (Model 3) among the presented variables.

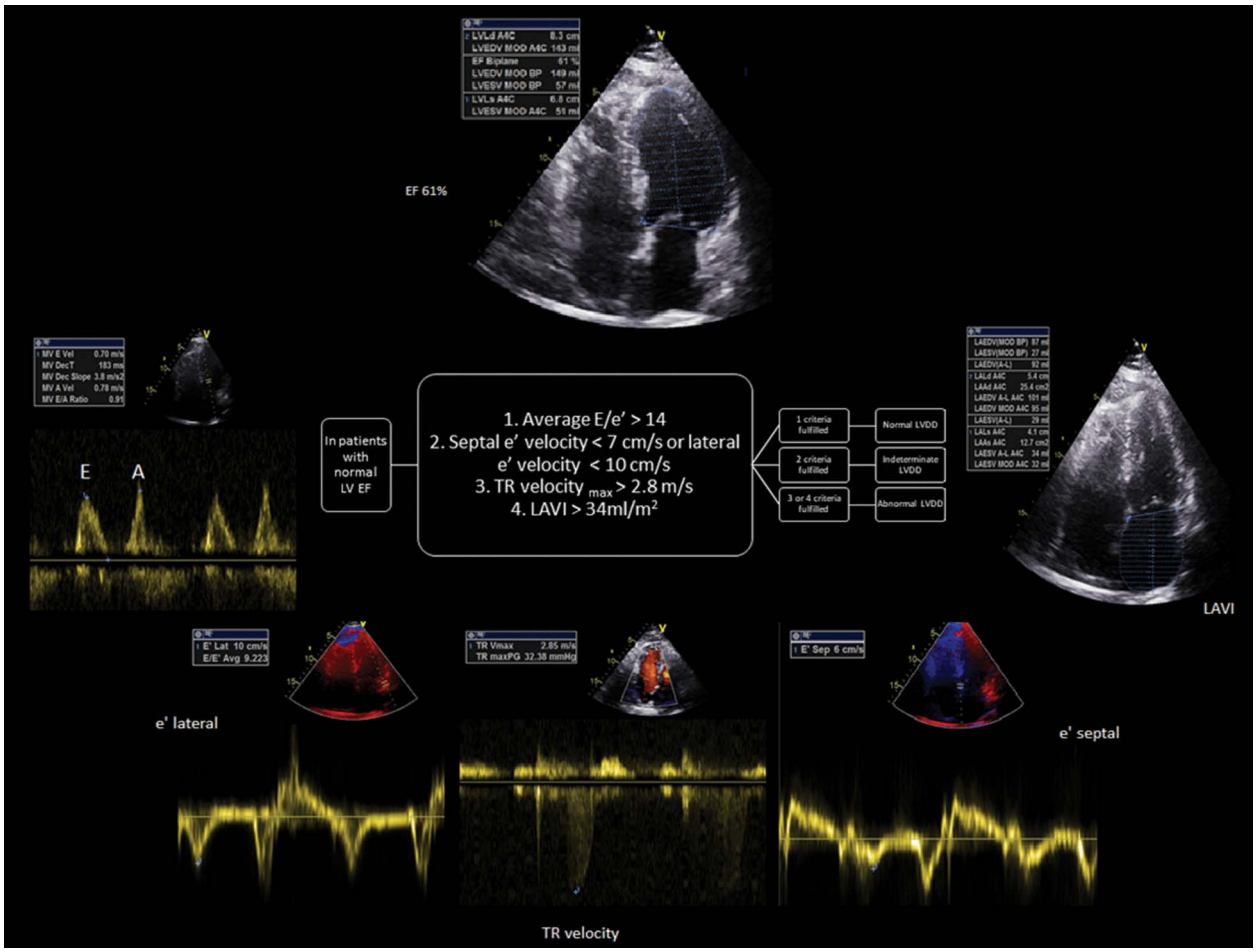

Figure 1. Transthoracic echocardiography images in a patient with the left ventricular diastolic dysfunction concerning European Association of Cardiovascular Imaging/American Society of Echocardiography (EACVI/ASE) 2016 recommendations

In logistic regression analysis with stepwise elimination of variables, the strongest independent factors associated with $LVDD_{2016}$ were BMI, hs-CRP, hs-TnT, LVEF and circumference of neck and waist (Table 5).

Discussion

These results indicate the importance of guidelines and the search for new markers influencing the phenomenon of LVDD. The present study provides evidence that BPd and hs-TnT parameters are related to $LVDD_{2016}$ regardless of age, gender, ejection fraction, and BMI. Another important result of the present analysis is the association between $LVDD_{2016}$ and anthropometric variables and steroid hormone (cortisol) even after considering several covariates. Inflammation marker (hs-CRP) independent of obesity was associated with $LVDD_{2016}$ as opposed to metabolic markers. Also, the differences in variables influencing diastolic disorders are presented depending on the guidelines used.

In this population, it was found that the prevalence of LVDD assessed by the 2016 method amounts to 5.4%. In other cohorts, including patients or parts of the general population, the incidence of LVDD varied widely, ranging from 28% to 39.1%, depending on the characteristics of the studied cohort as well as the LVDD definition [4, 5, 11–13]. This emphasizes the effect that different diagnostic algorithms and definitions may have for an appropriate description of LVDD in a particular population. According to Almeida et al. [14], in the general population without cardiovascular diseases, with a mean age of 62 ± 10.5 years, the incidence of LVDD and indeterminate diastolic dysfunction was assessed according to the latest recommendations was 16.6%. The author points out that the application of the new guidelines reduces the incidence and categorization of the degree of LVDD. This result contrasts with ours; however, given that the abovementioned study excluded participants younger than 45, it can be explained by older age. A similar conclusion to Almeida et al. [14] was reached by Prasad et al. [15]; who suggested that the lower prevalence of LVDD in large community-based cohorts is the result of the improved specificity of these guidelines. However, the authors emphasized that the results from the prognostic validation of algorithms

Table 2. Characteristics of the study population according to the presence of the left ventricular diastolic dysfunction

Variables		Subjects without any LVDD (90.1%) n = 584	Subjects with $LVDD_{1998}$ (4.5%) n = 29	Subjects with $LVDD_{2016}$ (5.4%) n = 35	P-value
General information	Age, years	46.59 ±14.71[b]	45.28 ± 15.25[c]	57.57 ± 12.72[b, c]	< 0.001
	Gender, male	246 (42.1)[a]	20 (69)[a]	17 (48.6)	0.015
	Exercise dyspnoea	38 (6.5)[b]	4 (13.8)	7 (20)[b]	0.008
	Exercise fatigue	86 (14.7)[b]	6 (20.7)	16 (45.7)[b]	< 0.001
	High CV risk class	70 (12.0)[b]	2 (6.9)[c]	9 (25.7)[b, c]	0.050
	Very high CV risk class	54 (9.2)[a, b]	6 (20.7)[a]	10 (28.6)[b]	0.001
	Current smoking	111 (19.0)	8 (27.6)	7 (20.0)	0.752
	Hypertension	213 (36.5)[b]	13 (44.8)[c]	23 (65.7)[b, c]	0.003
	Hypotensive medication	132 (22.6)[b]	8 (27.6)	14 (40.0)[b]	0.059
	History of diabetes mellitus	26 (4.5)[b]	3 (10.3)	4 (11.4)[b]	0.051
Blood pressure information	BPs, mm Hg	122.00 (110.50–134.63)[b]	127.00 (116.25–137.25)	133.50 (120.00–144.00)[b]	0.004
	BPd, mm Hg	80.50 (74.00–87.50)[b]	85.00 (74.75–90.75)	86.00 (80.50–96.50)[b]	0.001
	CPs, mm Hg	110.00 (100.00–121.00)[b]	104.00 (95.50–120.50)[c]	119.50 (106.00–143.25)[b, c]	0.002
	CPd, mm Hg	71.00 (65.00–79.00)	68.00 (59.50–79.50)	74.00 (70.00–82.00)	0.065
	PWV_{ba}, m/s	10.30 (9.00–11.70)[b]	9.70 (8.55–11.50)[c]	11.40 (9.93–13.45)[b, c]	0.007
Laboratory tests	Creatinine, mg/dL	0.76 (0.67–0.86)	0.82 (0.78–0.93)	0.76 (0.66–0.89)	0.025
	hs-CRP, mg/L	0.64 (0.30–1.47)[b]	0.53 (0.35–1.28)	1.10 (0.42–3.19)b	0.069
	NT-proBNP, pg/mL	49.44 (26.00–91.15)	36.09 (18.58–66.74)	68.77 (43.13–135.45)	0.022
	hs-TnT, pg/mL	5.91 (4.58–7.96)[b]	6.94 (5.56–9.29)[c]	8.53 (5.14–10.74)[b, c]	0.01
	Fasting glucose, mg/dL	99.00 (93.00–106.25)[b]	98.50 (90.25–105.5)[c]	105.00 (97.00–121.00)[b, c]	0.013
	120 min glucose, mg/dL	119.00 (100.00–139.00)[b]	113.00 (94.00–128.00)[c]	138.00 (109.00–167.00)[b, c]	0.016
	HbA1c, %	5.40 (5.10–5.70)[b]	5.40 (5.13–5.90)[c]	5.70 (5.30–6.00)[b, c]	0.001
	Cortisol, µg/dL	12.92 (9.95–16.26)	12.52 (10.68–14.20)	15.17 (12.54–20.10)	0.085
	IL-6, pg/mL	2.48 (1.92–3.57)	2.29 (1.84–3.46)	3.93 (2.73–6.77)	0.015

→

Table 2. (**cont.**) Characteristics of the study population according to the presence of the left ventricular diastolic dysfunction

Variables		Subjects without any LVDD (90.1%) n = 584	Subjects with $LVDD_{1998}$ (4.5%) n = 29	Subjects with $LVDD_{2016}$ (5.4%) n = 35	P-value
Body composition analysis	BMI, kg/m^2	25.77 (22.95–29.44)[b]	27.02 (24.84–30.76)	29.49 (25.49–32.88)[b]	0.001
	WHR	0.87 (0.80–0.94)	0.89 (0.83–0.95)	0.93 (0.84–0.99)	0.029
	FMI, kg/m^2	8.64 (6.68–10.75)[b]	7.74 (6.30–10.68)	10.65 (7.84–13.78)[b]	0.018
	LMI, kg/m^2	16.44 (14.88–18.26)[a, b]	17.87 (16.29–19.17)[a]	17.85 (16.28–19.42)[b]	0.001
	Neck, cm	36.00 (32.50–39.00)[b]	38.00 (34.50–40.25)	38.00 (35.88–41.25)[b]	< 0.001
	Waist, cm	86.21 ± 13.44[b]	90.40 ± 11.76	95.43 ± 13.89[b]	< 0.001
	Hips, cm	98.00 (92.50–104.50)[b]	99.00 (93.50–107.25)	104.00 (97.00–109.63)[b]	0.002
Echocardiography	LV ejection fraction, %	59.49 (56.28–62.46)[b]	59.65 (56.17–62.37)[c]	53.76 (49.33–58)[b, c]	< 0.001
	LVMI, g/m^2	71.26 (59.95–83.28)[b]	77.77 (65.74–91.04)	82.34 (70.61–97.27)[b]	0.001
	LAVI, mL/m^2	20.67 (17.28–25.38)[b]	22.68 (19.50–25.26)[c]	26.51 (19.08–36.65)[b, c]	0.001
	E/A	1.44 (1.13–1.83)[b]	1.38 (0.97–2.11)[c]	1.21 (0.87–1.50)[b, c]	0.01
	TR velocity $_{max}$, m/s	1.88 (1.21–2.20)	1.76 (1.61–2.00)	1.37 (0.85–2.07)	0.132
	e' sep, cm/s	9.49 (7.69–11.34)[b]	7.82 (6.72–10.27)	6.74 (5.89–8.44)[b]	< 0.001
	e' lat, cm/s	11.52 (9.31–14.53)[b]	11.29 (8.4–13.86)[c]	7.64 (6.28–9.76)[b, c]	< 0.001
	E/e'	6.64 (5.53–8.17)[b]	6.85 (5.83–8.07)[c]	9.32 (7.00–11.26)[b, c]	< 0.001

Data presented as mean ± standard deviation or median (Q1–Q3) or n (%); comparisons variables between subgroups, the same letters in each row ([a]between subjects without any left ventricular diastolic dysfunction (LVDD) and subjects with $LVDD_{1998}$; [b]between subjects without any LVDD and subjects with $LVDD_{2016}$; [c]between subjects with $LVDD_{1998}$ and subjects with $LVDD_{2016}$) represent significant differences at $p < 0,05$; A — peak velocity flow in late diastole caused by atrial contraction; BMI — body mass index; BPd — diastolic blood pressure; BPs — systolic blood pressure; CPd — diastolic central pressure; CPs — systolic central pressure; E — peak velocity flow in early diastole caused by atrial contraction; e' — early diastolic mitral annular tissue velocity; FMI — fat mass index; HbA1c — hemoglobin A1c; HDL — high-density lipoprotein; hs-CRP — C-reactive protein; hs-TnT — high-sensitivity troponin T; IL-6 — interleukin 6; lat — lateral; LAVI — left atrial volume index; LDL — low-density lipoprotein; LMI — lean mass index; LV — left ventricle; LVMI — left ventricular mass index; NT-proBNP — N-terminal pro-B-type natriuretic peptide; PWV_{ba} — brachial-ankle pulse wave velocity; sep — septal; TG — triglycerides; TR — tricuspid regurgitation; WHR — waist-to-hip ratio

2016 showed benefits for predicting clinical outcomes and improved consensus between observers across a broad range of observer experiences. In addition, the authors of the Euro-Filling study [16], comparing the 2009 and 2016 recommendations and relating them to invasive measurements of LV end-diastolic pressure, noted that the 2016 algorithm estimates left ventricular filling pressure better, yielding fewer false positives and more true positives.

The associations between LVDD and BMI or fat tissue distribution have been previously examined in population studies [5, 11]. Lee et al. [5] reported that LVDD, defined by the E/A ratio and E' velocity, was associated with increased BMI even after adjusting for clinical factors such as age, hypertension, diabetes, and LV hypertrophy. The present study also found this relationship, after adjusting for age, gender and ejection fraction, but only for $LVDD_{2016}$. In addition to the BMI, frequently described variables in the LVDD-related literature are waist circumference and abdominal fat distribution [12]. The presented study showed a significant association of LVDD with the body composition parameters. To the best of the authors' knowledge, this is the first study to investigate the association of LVDD with neck and hip circumferences. This study has shown that considering age, gender and ejection fraction, an increase in anthropometric measurements significantly increased the probability of the presence of $LVDD_{2016}$ in the general population.

Table 3. Univariable and multivariable predictors of left ventricular diastolic dysfunction assessed by the 2016 method

Variables	Unadjusted Model		Model 1: adjusted by age and sex		Model 2: Model 1 + LV ejection fraction		Model 3: Model 2 + BMI	
	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Age, years	< 0.001	1.054 (1.028;1.081)	–	–	–	–	–	–
Gender, male	0.455	1.298 (0.656;2.569)	–	–	–	–	–	–
LV ejection fraction, %	< 0.001	0.785 (0.722;0.853)	< 0.001	0.807 (0.740;0.879)	–	–	–	–
$LVMI_{BSA}$, g/m^2	< 0.001	1.034 (1.016;1.052)	0.033	1.022 (1.002;1.043)	0.049	1.022 (1.000;1.044)	0.169	1.016 (0.993;1.039)
BMI, kg/m^2	< 0.001	0.149 (0.057;0.390)	0.100	0.318 (0.081;1.245)	0.026	1.087 (1.010;1.170)	–	–
WHR*	0.526	1.280 (0.597;2.742)	0.933	1.034 (0.476;2.244)	0.517	1.193 (0.699;2.038)	0.602	0.842 (0.44;1.608)
FMI, kg/m^2	0.006	1.133 (1.036;1.238)	0.097	1.092 (0.984;1.211)	0.147	1.084 (0.972;1.210)	0.179	0.762 (0.513;1.133)
LMI, kg/m^2	0.008	1.214 (1.053;1.400)	0.027	1.245 (1.026;1.510)	0.030	1.270 (1.023;1.577)	0.272	1.240 (0.845;1.820)
Neck, cm	< 0.001	1.164 (1.074;1.260)	0.002	1.188 (1.064;1.326)	0.009	1.157 (1.036;1.291)	0.136	1.136 (0.961;1.344)
Waist, cm	< 0.001	1.048 (1.022;1.074)	0.021	1.036 (1.005;1.067)	0.037	1.033 (1.002;1.064)	0.801	1.010 (0.937;1.088)
Hips, cm	0.001	1.057 (1.023;1.093)	0.010	1.047 (1.011;1.085)	0.021	1.045 (1.007;1.085)	0.388	1.034 (0.959;1.114)
BPs, mm Hg	< 0.001	1.037 (1.018;1.056)	0.019	1.026 (1.004;1.047)	0.064	1.021 (0.999;1.044)	0.128	1.018 (0.995;1.041)
BPd, mm Hg	< 0.001	1.065 (1.031;1.099)	< 0.001	1.064 (1.027;1.102)	0.003	1.056 (1.019;1.094)	0.010	1.049 (1.011;1.088)
CPs, mm Hg	< 0.001	1.041 (1.020;1.062)	0.020	1.028 (1.004;1.052)	0.046	1.025 (1.000;1.050)	0.068	1.023 (0.998;1.048)
CPd, mm Hg	0.025	1.042 (1.005;1.080)	0.177	1.028 (0.988;1.069)	0.268	1.024 (0.982;1.068)	0.441	1.017 (0.974;1.063)
PWV_{ba}, m/s	0.001	1.292 (1.116;1.496)	0.216	1.126 (0.933;1.358)	0.914	1.011 (0.830;1.232)	0.747	1.034 (0.844;1.266)
hs-CRP, mg/L	0.057	1.058 (0.998;1.120)	0.125	1.045 (0.988;1.106)	0.034	1.065 (1.005;1.129)	0.039	1.065 (1.003;1.130)
NT-proBNP, pg/mL	0.224	1.002 (0.999;1.005)	0.619	0.999 (0.995;1.003)	0.423	0.998 (0.994;1.002)	0.511	0.999 (0.995;1.003)
hs-TnT, pg/mL	0.001	1.084 (1.032;1.138)	0.015	1.063 (1.012;1.117)	0.032	1.069 (1.006;1.136)	0.044	1.064 (1.002;1.130)
Fasting glucose, mg/dL	< 0.001	1.020 (1.010;1.031)	0.002	1.015 (1.006;1.025)	0.012	1.014 (1.003;1.025)	0.052	1.012 (1.000;1.023)
120 min glucose, mg/dL	0.003	1.012 (1.004;1.020)	0.256	1.005 (0.996;1.014)	0.151	1.007 (0.997;1.017)	0.243	1.006 (0.996;1.016)
HbA1c, %	< 0.001	1.970 (1.385;2.802)	0.032	1.542 (1.039;2.288)	0.079	1.428 (0.960;2.125)	0.195	1.320 (0.867;2.008)
Cortisol, µg/dL	0.038	1.066 (1.004;1.133)	0.021	1.083 (1.012;1.160)	0.042	1.078 (1.003;1.158)	0.010	1.096 (1.022;1.176)
IL-6, pg/mL	0.596	1.011 (0.970;1.054)	0.635	1.010 (0.968;1.054)	0.413	1.018 (0.975;1.064)	0.492	1.016 (0.971;1.063)

*Per 0.1 units; BMI — body mass index; BPd — diastolic blood pressure; BPs — systolic blood pressure; CI — confidence interval; CPd — diastolic central pressure; CPs — systolic central pressure; FMI — fat mass index; HbA1c — hemoglobin A1c; hs-CRP — C-reactive protein; hs-TnT — high-sensitivity troponin T; IL-6 — interleukin 6; LMI — lean mass index; LV — left ventricle; LVMI — left ventricular mass index; NT-proBNP — N-terminal pro-B-type natriuretic peptide; OR — odds ratio; PWV_{ba} — brachial-ankle pulse wave velocity; WHR — waist-to-hip ratio

Table 4. Univariable and multivariable predictors of left ventricular diastolic dysfunction assessed by 1998 method

Variables	Unadjusted model		Model 1: adjusted by age and sex		Model 2: Model 1 + LV ejection fraction		Model 3: Model 2 + BMI	
	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Age, years	0.640	0.994 (0.969;1.020)	–	–	–	–	–	–
Gender, male	0.006	3.053 (1.367;6.820)	–	–	–	–	–	–
LV ejection fraction, %	0.991	1.000 (0.924;1.083)	0.832	1.009 (0.932;1.092)	–	–	–	–
$LVMI_{BSA}$, g/m^2	0.110	1.016 (0.996;1.036)	0.452	1.009 (0.986;1.033)	0.453	1.009 (0.986;1.033)	0.562	1.007 (0.983;1.032)
BMI, kg/m^2	0.349	0.690 (0.317;1.501)	0.258	0.473 (0.129;1.729)	0.443	1.033 (0.950;1.123)	–	–
WHR*	0.872	1.075 (0.445;2.596)	0.913	1.053 (0.420;2.640)	0.356	0.756 (0.417;1.37)	0.147	0.599 (0.300;1.197)
FMI, kg/m^2	0.827	0.988 (0.885;1.102)	0.594	1.033 (0.916;1.165)	0.578	1.035 (0.917;1.168)	0.646	0.922 (0.650;1.306)
LMI, kg/m^2	0.010	1.226 (1.050;1.431)	0.326	1.112 (0.900;1.374)	0.322	1.113 (0.901;1.376)	0.527	1.117 (0.793;1.573)
Neck, cm	0.050	1.090 (1.000;1.188)	0.947	1.004 (0.888;1.136)	0.933	1.005 (0.888;1.138)	0.546	0.949 (0.800;1.125)
Waist, cm	0.102	1.023 (0.996;1.051)	0.707	1.007 (0.973;1.042)	0.694	1.007 (0.973;1.042)	0.501	0.973 (0.900;1.053)
Hips, cm	0.232	1.023 (0.986;1.061)	0.195	1.027 (0.987;1.069)	0.190	1.027 (0.987;1.069)	0.231	1.047 (0.971;1.129)
BPs, mm Hg	0.243	1.013 (0.991;1.035)	0.987	1.000 (0.974;1.027)	1.000	1.000 (0.974;1.027)	0.832	0.997 (0.970;1.025)
BPd, mm Hg	0.148	1.027 (0.991;1.065)	0.408	1.016 (0.979;1.054)	0.399	1.016 (0.979;1.054)	0.515	1.013 (0.975;1.053)
CPs, mm Hg	0.121	0.975 (0.945;1.007)	0.091	0.967 (0.929;1.005)	0.090	0.966 (0.929;1.005)	0.049	0.961 (0.923;1.000)
CPd, mm Hg	0.275	0.976 (0.934;1.020)	0.093	0.958 (0.911;1.007)	0.090	0.958 (0.911;1.007)	0.042	0.949 (0.902;0.998)
PWV_{ba}, m/s	0.227	0.866 (0.686;1.093)	0.149	0.806 (0.601;1.081)	0.138	0.799 (0.594;1.075)	0.165	0.810 (0.602;1.091)
hs-CRP, mg/L	0.391	0.872 (0.637;1.193)	0.484	0.897 (0.661;1.217)	0.477	0.896 (0.661;1.214)	0.383	0.854 (0.600;1.217)
NT-proBNP, pg/mL	0.199	0.995 (0.987;1.003)	0.444	0.997 (0.989;1.005)	0.445	0.997 (0.989;1.005)	0.464	0.997 (0.989;1.005)
hs-TnT, pg/mL	0.562	1.029 (0.934;1.134)	0.972	0.998 (0.893;1.116)	0.912	0.994 (0.888;1.112)	0.877	0.991 (0.883;1.112)
Fasting glucose, mg/dL	0.248	0.979 (0.945;1.015)	0.082	0.962 (0.920;1.005)	0.085	0.962 (0.920;1.005)	0.052	0.955 (0.911;1.000)
120 min glucose, mg/dL	0.080	0.987 (0.974;1.002)	0.102	0.988 (0.974;1.002)	0.103	0.988 (0.974;1.002)	0.103	0.988 (0.974;1.002)
HbA1c, %	0.648	1.136 (0.657;1.967)	0.578	1.180 (0.659;2.115)	0.566	1.187 (0.661;2.133)	0.651	1.150 (0.627;2.110)
Cortisol, µg/dL	0.434	0.968 (0.892;1.050)	0.314	0.954 (0.871;1.045)	0.314	0.954 (0.871;1.045)	0.338	0.955 (0.870;1.049)
IL-6, pg/mL	0.652	0.973 (0.866;1.095)	0.729	0.979 (0.866;1.106)	0.714	0.977 (0.864;1.105)	0.706	0.976 (0.861;1.107)

*Per 0.1 units; BMI — body mass index; BPd — diastolic blood pressure; BPs — systolic blood pressure; CI — confidence interval; CPd — diastolic central pressure; CPs — systolic central pressure; FMI — fat mass index; HbA1c — hemoglobin A1c; hs-CRP — C-reactive protein; hs-TnT — high-sensitivity troponin T; IL-6 — interleukin 6; LMI — lean mass index; LV — left ventricle; LVMI — left ventricular mass index; NT-proBNP — N-terminal pro-B-type natriuretic peptide; OR — odds ratio; PWVba — brachial-ankle pulse wave velocity; WHR — waist-to-hip ratio

Table 5. Results of stepwise backward logistic regression analysis of factors associated with the presence of left ventricular diastolic dysfunction defined by the 2016 method

Variables	Initial model		Final model	
	P-value	OR (95% CI)	P-value	OR (95% CI)
BMI, kg/m^2	0.052	1.363 (0.998;1.863)	0.003	1.403 (1.125 ± 1.749)
hs-CRP, mg/L	0.071	1.119 (0.990;1.265)	0.016	1.147 (1.026 ± 1.282)
hs-TnT, pg/mL	0.050	1.082 (1.000;1.172)	0.006	1.111 (1.031 ± 1.197)
LV ejection fraction, %	0.051	0.895 (0.801;1.000)	0.035	0.891 (0.801 ± 0.992)
Neck, cm	0.037	1.352 (1.018;1.796)	0.024	1.309 (1.036 ± 1.655)
Waist, cm	0.027	0.855 (0.744;0.982)	0.014	0.864 (0.768 ± 0.971)
BPd, mm Hg	0.046	1.061 (1.001;1.124)	0.089	1.046 (0.993 ± 1.102)
Age, years	0.272	1.027 (0.979;1.077)		
Fasting glucose, mg/dL	0.269	1.010 (0.992;1.029)		
Cortisol, µg/dL	0.243	1.064 (0.959;1.180)		
Gender, male	0.754	0.717 (0.089;5.741)		
Hips, cm	0.906	1.006 (0.905;1.119)		

R^2 Nagelkerke = 0.320; R^2 Cox-Snell = 0.111; BMI — body mass index; BPd — diastolic blood pressure; CI — confidence interval; hs-CRP — high-sensitivity C-reactive protein; hs-TnT — high-sensitivity troponin T; OR — odds ratio

The relationship between obesity and metabolic disorders is widely known; it is related to the fact that adipose tissue not only participates in energy storage but also acts as an endocrine organ that secretes bioactive substances. Ayalon et al. [17] found that metabolic syndrome was associated with LV diastolic dysfunction in a sample of individuals without existing cardiovascular disease. This association was independent of age, blood pressure, LV mass and BMI suggesting that obesity alone does not explain the association between metabolic syndrome and LVDD [17]. The present study showed that after considering the BMI, variables associated with metabolic disorders such as fasting and 120 min glucose, HbA1c were not significantly associated with LVDD. Obesity turned out to be a stronger predictor than fasting glucose.

Proinflammatory cytokines (such as hs-CRP, IL-6) contribute to the progression of HF through unfavourable effects on the vascular endothelium and at the myocyte level, they induce hypertrophy or enhance apoptosis [18]. Among the inflammatory markers that were included in the present study, only hs-CRP appeared to be strongly associated with $LVDD_{2016}$ in multivariable analysis. These results also suggest that the presence of inflammation is independent of obesity in people with diastolic disorders. No connection between inflammatory markers and $LVDD_{1998}$ was registered. Masiha et al. [6] showed that in the elderly population, CRP, and not IL-6, was associated with the LVDD parameter — E/A, the association was maintained after adjusting for hypertension and obesity.

Recently, hs-TnT has been introduced as a non-invasive marker for subclinical myocardial strain or injury. Ravassa et al. [19] revealed that the prevalence of LA enlargement, left ventricular hypertrophy (LVH) and LVDD increased with hs-TnT and NT-proBNP concentrations. Other researchers also confirmed the association of LVH with hs-TnT [20]. The present research is in line with the above studies, proving that elevated troponin level is associated with $LVDD_{2016}$, which could indicate a worse prognosis for this population. Contrary to other reports [4, 19] this study did not show a relationship between LVDD and NT-proBNP. Differences may be due to different group characteristics or a different LVDD definition. Another population-based study in which

participants underwent routine follow-up and which pre-excluded any echocardiography-detected valvular heart disease was excluded, also found no link between preclinical diastolic dysfunction and NT-proBNP [21].

Finally, cortisol is a steroid hormone, and its release is increased in response to stress and low blood-glucose concentration, but it can also have a direct relevant influence on cardiac function [22]. Sbardella et al. [23] revealed that in apparently asymptomatic patients, mild autonomous cortisol secretion can sustain early cardiac and vascular remodelling, independently of other risk factors. This study confirmed a significant relationship between LVDD and cortisol even after adjusting for age, sex, LVEF and BMI. On the other hand, it is known that patients with abdominal obesity have elevated cortisol levels [24]. The consequences will most likely be more expressed in visceral than subcutaneous adipose tissues because of higher cellularity, innervation and blood flow [25]. This may explain why in stepwise multivariate regression analysis, which included markers of android type fat distribution it was not possible to find a significant association between LVDD and cortisol levels. Based on this study it is hypothesized that LVDD's relation to android type obesity may be due to increased cortisol concentration.

Overall, LVDD assessment remains to be a challenge, although the latest guidelines seek to simplify its implementation in daily practice. Further work on improving and updating the 2016 algorithm and validating echocardiographic parameters against left heart cardiac catheterization in large populations like Euro-Filling [16], will allow for better detectability and a deeper understanding of the phenomenon of diastolic disorders, trying to prevent the development of HF.

This study has several limitations. First, the prevalence of diastolic dysfunction is low. Therefore, LVDD indeterminate was combined with abnormal and analysed as one group. Another, follow up has not been conducted yet, so there is no information on how diastolic dysfunction will develop further in these participants. Lastly, this study includes a subset of the population, a group of potentially healthy individuals. A large group of people who were very likely to have LVDD was excluded.

Conclusions

Assessment of obesity using simple, cheap and generally available methods, such as BMI, neck circumference or waist circumference, as well as the determination of hs-TnT and hs-CRP can be used to detect people at a greater risk of LVDD in the general population. In a larger population, it would be advisable to estimate the cut-off points of these parameters for the assessment of the risk of LVDD.

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Conflict of interest

None declared.

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Streszczenie

Wstęp: Dysfunkcję rozkurczową lewej komory (LVDD) opisuje się jako upośledzoną relaksację lewej komory (LV) i zmniejszoną jej podatność. W literaturze dostępne są rozbieżne dane na temat częstości występowania LVDD ze względu na różne definicje. Celem pracy była ocena częstości występowania LVDD w populacji bez ciężkiej choroby układu sercowo-naczyniowego (CVD), a także identyfikacja czynników z nią związanych.

Materiał i metody: Włączono 648 osób bez istotnej CVD. Dysfunkcję rozkurczową lewej komory oceniono przy użyciu ostatnich wytycznych z 2016 roku ($LVDD_{2016}$) oraz poprzednich zaleceń z 1998 roku ($LVDD_{1998}$).

Wyniki: 35 uczestników (5,4%) spełniło kryteria $LVDD_{2016}$, a 29 osób (4,5%) spełniło tylko kryteria $LVDD_{1998}$. Najsilniejszymi czynnikami niezależnie związanymi z $LVDD_{2016}$ były wskaźnik masy ciała (BMI), stężenie białka C-reaktywnego oraz troponiny T oznaczonych metodami wysokoczułymi, frakcja wyrzutowa LV oraz obwód szyi i talii.

Wnioski: Częstość LVDD według wytycznych z 2016 roku w populacji bez ciężkiej CVD wynosi 5,4%. Jej obecność jest związana z markerami zapalnymi, uszkodzeniami serca oraz parametrami antropometrycznymi typowymi dla otyłości.

Słowa kluczowe: dysfunkcja rozkurczowa lewej komory, echokardiografia, badanie populacyjne, czynniki ryzyka

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