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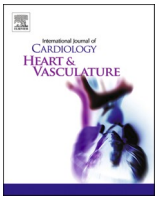

Relation between cardiac magnetic resonance-assessed interstitial fibrosis and diastolic dysfunction in heart failure due to dilated cardiomyopathy

Ewa Dziewięcka [a,b], Mateusz Winiarczyk [a,b], Robert Banyś [c], Małgorzata Urbańczyk-Zawadzka [c], Maciej Krupiński [c], Małgorzata Mielnik [c], Sylwia Wiśniowska-Śmiałek [a,b,d], Aleksandra Karabinowska-Małocha [a,b], Agata Leśniak-Sobelga [a,b], Katarzyna Holcman [a,b], Magdalena Kostkiewicz [a,b], Marta Hlawaty [a,b], Piotr Podolec [a,b], Jan Robak [e], Monika Kaciczak [e], Filip Baranowski [e], Paweł Rubiś [a,b,*]

[a] *Clinical Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Collegium Medicum, Cracow, Swietej Anny Street 12, Cracow, Poland*
[b] *Department of Cardiac and Vascular Diseases, Saint John Paul II Hospital in Cracow, Prądnicka Street 80, 31-202 Cracow, Poland*
[c] *Department of Radiology, Saint John Paul II Hospital in Cracow, Prądnicka Street 80, 31-202 Cracow, Poland*
[d] *Department of Cardiovascular Surgery and Transplant, Saint John Paul II Hospital in Cracow, Prądnicka Street 80, 31-202 Cracow, Poland*
[e] *Students' Scientific Group at the Department of Cardiac and Vascular Diseases, Jagiellonian University Collegium Medicum, John Paul II Hospital, Prądnicka Street 80, 31-008 Krakow, Poland*

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ABSTRACT

Background: Dilated cardiomyopathy (DCM) is distinguished by left ventricle (LV) dilation accompanied by systolic dysfunction. However, some studies suggested also a high prevalence of LV diastolic dysfunction (LVDD), similar to a general cohort of heart failure (HF) with reduced ejection fraction (LVEF). The bulk of evidence, mostly arising from basic studies, suggests a causative link between cardiac fibrosis (CF) and LVDD. However, still, there remains a scarcity of data on LVDD and CF. Therefore, the aim of the study was to investigate the association between CF and LVDD in DCM patients.

Methods: The study population was composed of 102 DCM patients. Replacement CF was evaluated qualitatively (late gadolinium enhancement – LGE) and quantitively (LGE extent); interstitial cardiac fibrosis was assessed via extracellular volume (ECV). Based on echocardiography patients were divided into normal and elevated left atrial pressure (nLAP, eLAP) groups.

Results: 42 % of patients had eLAP. They displayed higher troponin and NT-proBNP. Both groups did not differ in terms of LGE presence and extent; however, eLAP patients had larger ECV: 30.1 ± 5.6 % vs. 27.8 ± 3.9 %, $p = 0.03$. Moreover, ECV itself was found to be an independent predictor of LVDD (OR = 0.901; 95 %CI 0.810–0.999; $p = 0.047$; normalised for LVEF and RVOT diameter).

Conclusions: More than two-in-five DCM patients had at least moderate LVDD. The mere presence or extent of replacement cardiac fibrosis is similar in patients with nLAP and eLAP. On the other hand, interstitial cardiac fibrosis is more pronounced in those with a higher grade of LVDD. ECV was found to be an independent predictor of LVDD in DCM.

Abbreviations: (%)LGE, (extent of) late gadolinium enhancement; AUC, area under curve; CF, cardiac fibrosis; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; EACVI, European Association of Cardiovascular Imaging; ECV, extracellular volume; HF(m)rEF/pEF, heart failure with (mildly) reduced/preserved ejection fraction; hsTnT, high-sensitive troponin T; nLAP/eLAP, normal and elevated left atrial pressure; NYHA, New York Heart Association class; IVS, intraventricular septum; LAVI, left atria volume indexed; LGE, late gadolinium enhancement; LVDD, left ventricle diastolic dysfunction; LVEF, left ventricle ejection fraction; LVSD, left ventricular systolic dysfunction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; TRV, tricuspid regurgitation velocity.

* Corresponding author at: Department of Cardiac and Vascular Diseases, Jagiellonian University Collegium Medicum, John Paul II Hospital, Prądnicka Street 80, 31-202 Krakow, Poland.
E-mail address: pawelrub@poczta.onet.pl (P. Rubiś).

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1. Background

Left ventricular systolic dysfunction (LVSD) is the hallmark of heart failure (HF), and based on ejection fraction (LVEF), patients are stratified into three phenotypes [1]. Nonetheless, its counterpart, LV diastolic dysfunction (LVDD), which is present in at least half of patients with HF with reduced LVEF (HFrEF), should not be regarded as a mere "innocent bystander" [2]. On the contrary, LVDD has been shown to have a negative effect on the clinical course and outcomes in HFrEF and HF with mildly reduced EF (HFmrEF) [2].

Dilated cardiomyopathy (DCM), being a leading cause of HF in young adults, is a progressive myocardial disease, distinguished by LV dilation accompanied by varying degrees of LVSD [1,3]. Thus, if an LVEF-based scoring system is applied, DCM patients are accordingly qualified for HFrEF and HFmrEF phenotypes. However, when it comes to the subject of LVDD itself, including its prevalence, pathology, and clinical or prognostic significance, this is a matter that has been as yet poorly explored in DCM.

The most recent joint recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (EACVI) provide an updated algorithm for the diagnosis of LVDD [4]. Based on the interplay of numerous diastolic function parameters, patients are divided into two LVDD severity grades: those with normal and elevated left atrial pressure (nLAP, eLAP).

The bulk of evidence, mostly arising from basic studies, suggests a causative link between cardiac fibrosis (CF) and LVDD. It is known that CF results from changes in the myocardial extracellular matrix, including the accumulation of excessive collagens and other fibrillar proteins; this, in turn, leads to impaired LV relaxation and increased stiffness, which is ultimately the cause of LVDD [5,6]. However, in most of these studies, CF was assessed in small myocardial samples derived from endomyocardial biopsy, either from animal models or from small groups of patients, mostly with HF with preserved LVEF (HFpEF). Nowadays, in contrast to those types of invasive techniques, what is currently used for non-invasive and robust investigations of the heart's morphology, including CF, is cardiac magnetic resonance (CMR) with high correlation to invasive measurements and prognostic significance [7–9]. Recent developments in CMR allow for the quantitative assessment of both replacement and interstitial CF, two phenomena which, in all likelihood, have differing pathologies and clinical meanings [10,11]. Still, there remains a scarcity of data on LVDD and CF in HF and DCM in particular.

Thus, the main purpose of the study was to explore the - so far - unknown association between LVDD and CMR-assessed CF, both replacement and interstitial, in HFrEF and HFmrEF due to DCM.

2. Methods

2.1. Study population

We included 102 DCM patients 18–65 years old in this prospective, single-centre observational study, all of whom had stable HF symptoms (NYHA I-III class) between May 2019 and September 2020. DCM was diagnosed in accordance with the current recommendations of the European Society of Cardiology (ESC), based on (1) LV dilation (detected via echocardiogram or CMR), (2) impaired LV systolic function (LVEF $<$ 45 %), after the exclusion of (a) significant coronary artery disease, (b) primary heart valve disease, (c) congenital heart disease, and (d) severe arterial hypertension (presence of resistant hypertension or hypertension requiring complex treatment with concomitant LV hypertrophy) [1,12,13]. Patients with acute diseases (such as myocarditis or pericarditis) or severe chronic diseases (like neoplasm, liver or kidney diseases), were excluded from the study. All patients underwent a detailed diagnostic work-up, including laboratory tests, electrocardiography, transthoracic echocardiography and CMR, and all of them received guideline-approved optimal HF therapy [1].

The study protocol was approved by the John Paul II Institutional Review Board and the Krakow Medical Chamber Ethics Committee (reference number 7/KBL/OIL/2019). All of the patients gave written informed consent. All of the study-related procedures were performed in line with the current Guidelines for Good Clinical Practice and the 2013 Declaration of Helsinki.

2.2. Cardiac magnetic resonance protocol

CMR exams were conducted on a 3.0-T scanner (Magnetom Skyra, Siemens, Erlangen, Germany) at the time of inclusion, between 2 and 3 days after echocardiographic assessment. Standard CMR examination for anatomical and functional assessment consisted of a cine images in a short-axis stack and 2-, 3-, and 4-chamber long-axis views using an electrocardiogram-gated steady-state free precession sequence. Typical imaging parameters were: slice thickness of 8 mm with 2 mm gap between slices. T1-mapping using a Modifed Look-Locker Imaging technique (MOLLI) with motion correction was performed before and at 15 min after intravenous injection of 0.1 mmol/kg of body weight of gadolinium-based contrast agent. The following typical MOLLI sequence tfi2Dl parameters were used: breath-hold TR/TE of 281/1.1 ms, slice thickness of 8 mm, FOV from 320 $\times$ 260 mm^2, matrix of 144 $\times$ 256 pixels, and a flip angle of 35°. T2 mapping was acquired using a T2-prepared single-shot bSSFP sequence in basal, mid and apical ventricular short-axis slices (identical to T1 mapping) before the contrast agent injection. Each acquisition of T1- and T2-mapping was adapted depending on the ECG recording.

2.3. CMR image analysis

Two independent observers analysed the images on a dedicated workstation using commercial software with Syngo.VIA version VB 40 (Siemens, Erlangen, Germany) in compliance with the Society of Cardiovascular Magnetic Resonance [14]. Cardiac volumetric and functional parameters were quantified based on manual detection of the endocardial and epicardial borders using a stack of continuous short-axis slice cine images. LV and RV masses were measured by manually delineating the endocardial borders of each short-axis slice at end-diastole and during each cardiac phase between end-systole and diastasis. Papillary muscles and trabeculae were included as part of the ventricular lumen. Images of late gadolinium enhancement (LGE) were a qualitative assessment for the presence and extent of hyperintense lesions if present in both short and long-axis views. T1-time was assessed pre- and post-contrast by region of interest (ROI) of about 5 mm placed in every LV segment (with the exclusion of regions with LGE), using the AHA 16-segment model of the heart. Segments with artefacts, including poor breath holding, cardiac motion and off-resonance artefacts, possibly leading to inaccurate T1 measurements, were excluded. Extracellular volume (ECV) was calculated based on pre- and post-contrast T1-times of myocardium and blood pool, and haematocrit (assessed on the same day as CMR) as the mean of all LV segments according to the established formula: ECV = ((1/(postcontrast T1) − 1/(native T1))/(1/(blood postcontrast T1)) − 1/(blood native T1))*(1 − Hct) [15]. Based on T2-mapping presence of myocarditis was assessed. As reported previously, T1 and T2 measurements had high reproducibility [15].

2.4. Echocardiography

All echocardiographic examinations were performed on commercially available equipment (Philips Affinity 70, Philips, Amsterdam, The Netherlands; with sector transducer 1–5 MHz Philips S5-1 sector) by experienced echocardiographers. Chamber dimensions and wall thicknesses were measured following the recent EACVI recommendations [4,16–18].

LV inflow parameters – early (E wave) and late diastolic flow velocity

(A wave), were evaluated by pulsed-wave Doppler from the apical 4-chamber view with the sample volume placed between the tips of mitral leaflets. Tissue Doppler mitral annular early diastolic velocities (e') were measured at the septum and lateral wall and were averaged for calculation of the E/e' ratio. Parasternal and apical four-chamber views were used to obtain the highest tricuspid regurgitation velocity (TRV) aligned with continuous-wave Doppler.

Based on those measurements patients were divided into normal or mildly impaired LVDD (G1) – with normal LAP (nLAP), and at least moderate or severe LVDD (G2/G3) – with eLAP (Fig. 1).

2.5. Statistical analysis

All values are presented as either *mean ± standard deviations* or *percentages (counts)*. The Shapiro–Wilk test was used for the analysis of the normal distribution of quantitative variables. The comparisons of the continuous variables were conducted with a *t*-test or a U-Mann-Whitney test when appropriate, and the comparisons of the qualitative parameters were carried out using the $\chi 2$ test. The correlation analyses were conducted based on a Pearson correlation for variables with normal distribution; otherwise, the Spearman rank correlation was employed. All parameters from Tables 1 and 2 differentiating nLAP and eLAP groups (with $p < 0.10$) were included in the regression analyses. The associations between these parameters and diastolic function were analysed with uni- and multivariable logistic regression methods. The logarithmic transformation of high-sensitive troponin T (hs-TnT) and NT-proBNP were utilised for logistic regression models. Redundant parameters (correlated with other predictors with $R > 0.45$) were not included in the multivariable regression models; "RAA/BSA" was not included in the multivariable analysis due to a strong correlation with "RVOT/BSA" [$R = 0.48$, $p < 0.05$], NT-proBNP - due to a strong correlation with LVEF [$R = 0.55$, $p < 0.05$] and troponin T (TnT) - with ECV [$R = 0.50$, $p < 0.05$]. Areas under the receiver operating curve (ROC), referred to as AUC, were calculated in order to assess the cut-off values of ECV for the presence of LVDD. All results were considered statistically significant when the p-value was < 0.05. The Statistica package, version 13.3 (StatSoft, TIBCO Software Inc., Palo Alto, CA, USA), was used for the statistical analysis.

3. Results

3.1. Baseline characteristics of the prospective population

There were 43 (42 %) patients with eLAP, who had more pronounced LV remodelling with worse LVSD, but with no right ventricle systolic dysfunction. Neither group differed in terms of clinical presentation and comorbidities, including NYHA class. However, eLAP patients had higher troponin and NT-proBNP levels (Table 1).

3.2. Comparison of CMR results between DCM patients with normal and elevated LAP

When comparing the groups, no differences were found in replacement CF parameters (assessed either qualitatively – LGE presence, or quantitatively – LGE extent; %LGE) (Table 2). Although, numerically more patients in eLAP group had LGE. Moreover, the mean ECV of all segments, representing interstitial fibrosis, differed significantly between groups (Fig. 2-B). Of note was the finding that not every ECV of the separate segments were different (Table S1). Moreover, when analysing LGE presence separately for each LV segment, no difference

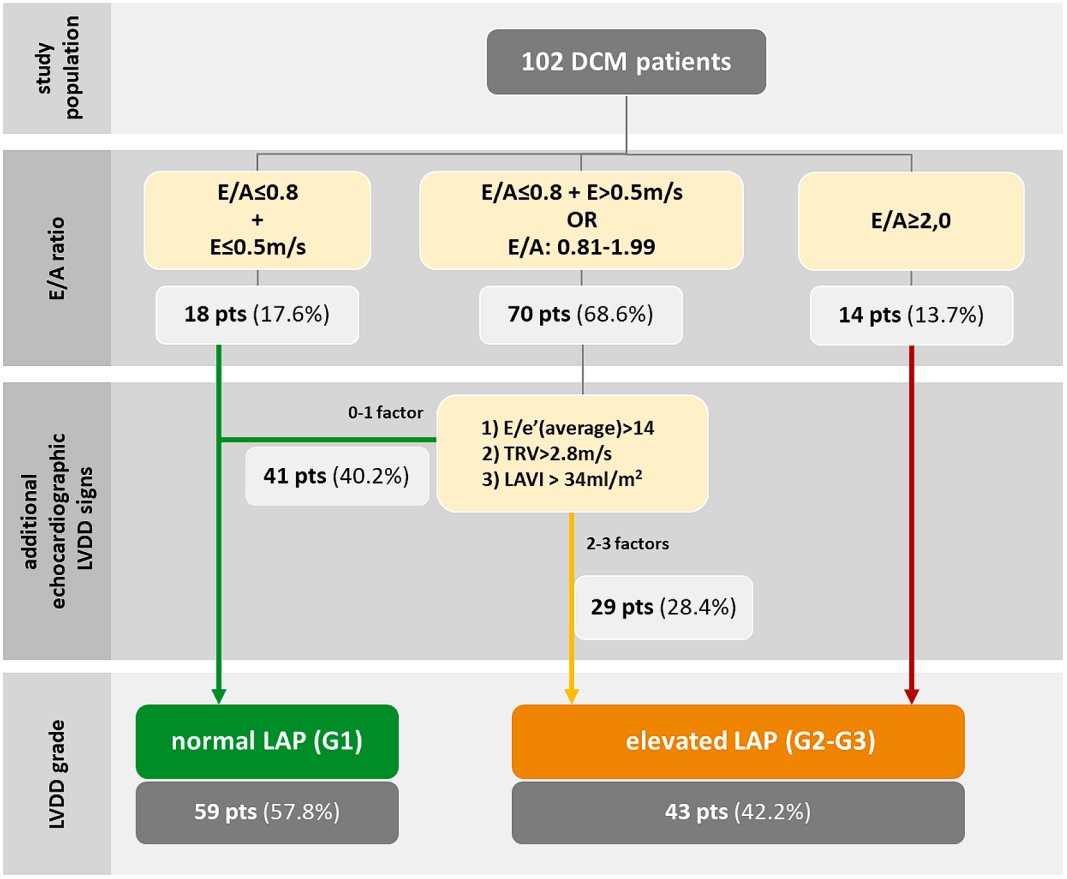

Fig. 1. Left ventricle diastolic function assessment with echocardiography. *Abbreviations: G1 – normal or mildly abnormal LV diastolic function, G2 – moderate or severe LV diastolic dysfunction, LAP – left atria pressure, LAVI – left atria volume index, LVDD – left ventricle diastolic dysfunction, TRV - peak tricuspid regurgitation velocity.*

Table 1
Baseline characteristics. Comparison between groups with normal and elevated left atrial pressure (eLAP vs. nLAP).

	nLAP (n = 59; 57.8 %)	eLAP (n = 43; 42.2 %)	p-value
CLINICAL PARAMETERS			
Male [n, %]	53 (89.8 %)	36 (83.7 %)	0.36
Age [years]	45.09 ± 12.19	45.42 ± 11.29	0.90
BMI [kg/m^2]	27.80 ± 5.37	29.41 ± 6.00	0.17
NYHA class	1.75 ± 0.60	1.88 ± 0.65	0.51
HF symptoms' duration [months]	15.46 ± 20.07	17.22 ± 27.37	0.45
Distance in 6MWT [m]	455.95 ± 90.36	432.91 ± 92.29	0.64
Systolic/diastolic blood pressure [mmHg]	118.9 ± 17.1/ 75.4 ± 12.5	121.4 ± 22.1/ 79.5 ± 14.4	0.95/ 0.24
COMORBIDITIES			
Atrial fibrillation [n, %]	14 (23.7 %)	13 (30.2 %)	0.46
Diabetes mellitus [n, %]	9 (15.3 %)	6 (14.0 %)	0.85
Dyslipidemia [n, %]	35 (59.3 %)	28 (65.1 %)	0.55
Hypertension [n, %]	12 (20.3 %)	9 (20.9 %)	0.94
Chronic obstructive pulmonary disease [n, %]	4 (6.8 %)	2 (4.7 %)	0.65
Prior stroke [n, %]	1 (1.7 %)	0 (0 %)	0.39
Obstructive sleep apnoea [n, %]	2 (3.4 %)	1 (2.3 %)	0.75
ELECTROCARDIOLOGICAL PARAMETERS			
Heart rate [bpm]	68.41 ± 9.51	70.34 ± 9.55	0.46
QRS [ms]	100.00 ± 26.20	101.43 ± 28.51	0.75
LBBB [n, %]	11 (18.6 %)	5 (11.6 %)	0.34
Ventricular tachycardia [n, %]	15 (25.4 %)	17 (39.5 %)	0.10
ECHOCARDIOLOGICAL PARAMETERS			
LVEDd/BSA [mm/m^2]	31.13 ± 4.65	32.20 ± 5.00	0.16
LVEF [%]	31.41 ± 9.52	27.27 ± 10.29	0.04
RVOT/BSA [mm/m^2]	16.76 ± 2.32	18.05 ± 3.01	0.007
TAPSE [mm]	19.62 ± 3.66	19.40 ± 4.58	0.59
RV fractional area change [%]	33.31 ± 17.12	37.55 ± 13.05	0.72
Lad [mm]	39.81 ± 8.47	49.88 ± 8.49	<0.001
LAVI [ml/m^2]	43.90 ± 17.51	68.86 ± 31.54	<0.001
RAA/BSA [cm^2/m^2]	9.22 ± 2.12	11.33 ± 3.54	<0.001
E wave [m/s]	0.64 ± 0.21	0.94 ± 0.21	<0.001
E/A ratio	0.93 ± 0.40	1.97 ± 0.96	<0.001
Significant mitral regurgitation [n, %]	14 (23.7 %)	22 (51.2 %)	0.004
e' (lateral) [cm/s]	9.21 ± 3.35	8.91 ± 4.78	0.28
e' (IVS) [cm/s]	6.43 ± 2.27	7.07 ± 3.64	0.49
E/e'	8.62 ± 3.30	12.86 ± 7.41	<0.001
Significant tricuspid regurgitation [n, %]	2 (3.4 %)	9 (20.9 %)	0.005
TRV [m/s]	1.91 ± 1.04	3.31 ± 1.41	<0.001
LABORATORY PARAMETERS			
Haemoglobin [g/dl]	14.64 ± 1.54	14.80 ± 1.60	0.79
Creatinine [μmol/l]	91.68 ± 20.64	91.47 ± 46.40	0.23
Uric acid [μmol/l]	413.32 ± 104.02	435.59 ± 129.43	0.55
LDL cholesterol [mmol/l]	3.09 ± 0.97	3.08 ± 0.82	0.99
Fasting glucose [mmol/l]	5.60 ± 0.84	6.07 ± 2.02	0.51
TSH [μU/ml]	2.27 ± 1.28	2.10 ± 1.36	0.36
hs-troponin T [ng/ml]	0.01 ± 0.01	0.04 ± 0.17	0.02
NT-proBNP [pg/ml]	638 ± 729	1776 ± 1923	<0.001
HEART FAILURE THERAPY			
RAAS inhibitors [n, %]	58 (98.31 %)	43 (100 %)	0.39
Beta-blockers [n, %]	59 (100 %)	43 (100 %)	1.00
Mineralocorticoid receptor antagonists [n, %]	56 (94.9 %)	42 (97.7 %)	0.48
SGLT2 inhibitors [n, %]	5 (8.5 %)	4 (9.3 %)	0.88
Loop diuretics daily dosage [mg/day]	29.37 ± 33.77	53.50 ± 84.16	0.11

Abbreviations: 6MWT – 6-minute walk test, BMI – body mass index, BSA – body surface area, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, LVEDd – left ventricle end-diastolic diameter, Lad – left atria diameter, LAVI – left atria volume indexed, LDL – low-density lipoprotein, LVEF – left ventricle ejection fraction, hs- – high-sensitive, NYHA – New York Heart Association class, RAA – right atria area, RAAS – renin-angiotensin-aldosterone system inhibitors (angiotensin receptor-neprilysin inhibitor or angiotensin-converting-enzyme inhibitor), RV – right ventricle, RVOT – right ventricle outflow tract diameter, TAPSE – tricuspid annular plane systolic excursion, TAPSE – tricuspid annular plane systolic excursion, TRV – tricuspid regurgitation peak velocity, TSH – thyroid-stimulating hormone.

Table 2
A comparison of the CMR results between groups with normal and elevated left atrial pressure.

	nLAP (n = 59)	eLAP (n = 43)	p-value
RV mass [g]	45.54 ± 13.55	49.12 ± 21.12	0.81
LV mass [g]	176.17 ± 52.10	191.50 ± 50.94	0.12
LAA [cm^2]	24.7 ± 6.4	31.3 ± 8.1	<0.001
LGE [n, %]	23 (39.0 %)	21 (48.8 %)	0.30
LGE mass [g]	3.55 ± 8.39	4.39 ± 7.33	0.28
LGE extent [%]	4.92 ± 5.92	4.16 ± 3.97	0.99
T1-time native [ms]	1214.30 ± 185.73	1279.23 ± 69.63	0.04
T1-time postcontrast [ms]	470.79 ± 48.40	471.14 ± 50.64	0.97
T1-time native blood [ms]	1762.72 ± 284.69	1835.94 ± 114.06	0.56
T1-time postcontrast blood [ms]	303.52 ± 42.75	322.17 ± 53.60	0.08
ECV [%]	27.78 ± 3.94	30.10 ± 5.62	0.03

Abbreviations: ECV – extracellular volume, LGE – late gadolinium enhancement, LV – left ventricle, nLAP/eLAP – normal/elevated left atria pressure, RV – right ventricle.

between the groups was found (all $p > 0.05$; Fig. 2-A, Tables S2-3).

3.3. Relation between cardiac fibrosis and diastolic function

Out of all echocardiographic diastolic parameters, only left atria volume indexed (LAVI) mildly correlated with ECV (LAVI: $R = 0.27$, $p = 0.01$) while no parameter correlated with %LGE (Table S4). In addition, ECV alone was found to be an independent predictor of LVDD; furthermore, it was associated with an 11 % increase in LVDD risk for every increase in ECV of 1 % (in the model with LVEF and indexed right ventricle outflow tract) (Table S5). Individually, ECV had a moderate impact on the degree of LVDD (AUC 0.634 [95 %CI 0.517–0.751], $p = 0.03$).

4. Discussion

The study findings can be summarized as follows: 43 % of DCM patients display elevated LAP. Patients with more advanced LVDD had larger right ventricles and both atria, worse LV systolic function and higher HF biomarkers; however, they did not differ in terms of clinical status, NYHA class and distance in 6-minute walk test, comorbidities and HF therapy. Replacement CF was not associated with LVDD whereas ECV, a marker of interstitial CF, was found to be a factor responsible for the profound impairment of LV diastolic function.

What can be surprising in terms of the results, nLAP and eLPA patients did not differ in terms of age, comorbidities, most of the classic HF parameters – HF symptoms severity and duration, clinical status (heart rate, blood pressure), presence of bundle branch blocks, LV size. However, the population was quite young with a mean age of 45 years, with only a few comorbidities (except for dyslipidemia). Moreover, HF therapy was initiated in nearly every patient, probably resulting in good clinical status and less advanced HF symptoms. However, most objective HF parameters, like NT-proBNP, TnT echocardiographic cardiac remodelling parameters, and numerically more common ventricular tachyarrhythmias, were significantly worse in eLAP group.

Taking a broader perspective, the "classic" consensus would assert

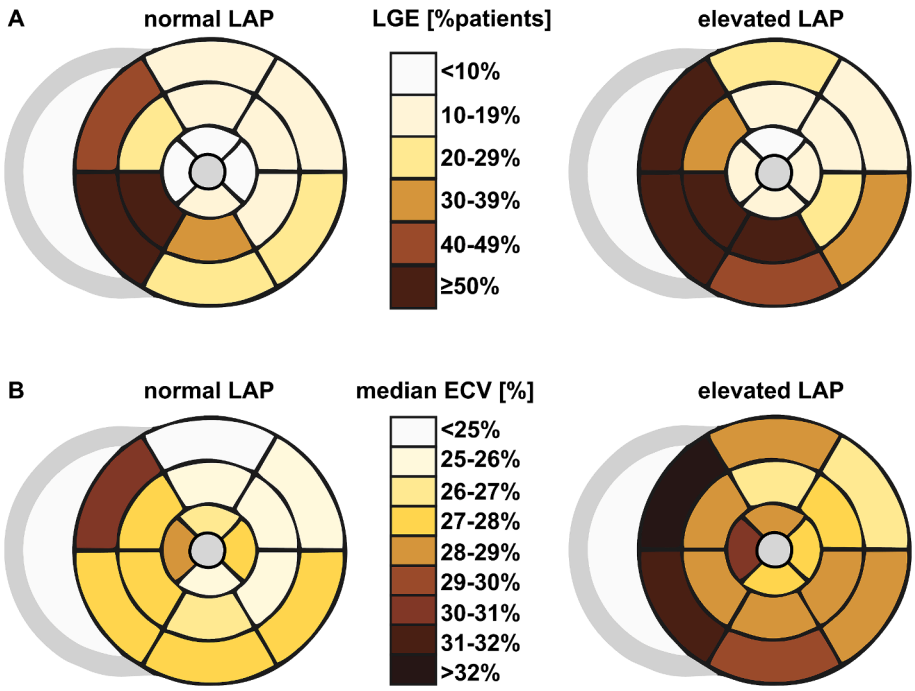

Fig. 2. Differences in DCM patients with different grades of left ventricular diastolic dysfunction (LVDD). *Differences in LVDD between LV replacement (2-A: late gadolinium enhancement - LGE presence in each segment of all patients with LGE) and interstitial fibrosis (2-B: median extracellular volume - ECV).*

that any excessive extracellular myocardial deposition of fibrillar proteins leads to an increased LV stiffness and relaxation impairment, which are then responsible for the development of LVDD [19]. Certainly, it is true that this "universal" pattern is observed in numerous heart diseases of various aetiologies, including hypertension- and diabetes-induced HFpEF, ischemic heart disease or aortic stenosis [20–22]. Hence, it is not really a surprise that there is the view that "ubiquitous" CF in HFrEF/HFmrEF and DCM leads to pronounced LVDD. However, in actuality, there is scant data that clearly confirms such a relationship. The only data that exists on the association between CF and LVDD in HFrEF of ischemic aetiology comes from invasive studies (hemodynamic measurements and endomyocardial biopsies) performed in the 1980s on small populations [23,24]. Here it is important to emphasize the fact that DCM patients are remarkably different from the rest of the ischemic HFrEF population in terms of age of presentation and clinical course, including a higher likelihood of LV reverse remodelling, fewer comorbidities and a better response to HF therapy [25–27]. Currently, the preferable method for CF assessment is CMR, which uniquely allows for two types of CF assessment – replacement and interstitial; it is notable that this was not the case in the historical studies that relied solely on biopsies.

Surprisingly, there is also little data exploring the subject of LVDD in DCM. Mojca et al. found that nearly 50 % out of 38 DCM patients had LVDD, which is in line with our findings [28]. To the best of our knowledge, there has been only one study focusing on the problem of replacement CF and LVDD in DCM. Malaty et al. observed significant differences in terms of LV diastolic echocardiographic parameters between patients with LGE; however, the study was performed in 2010, therefore, LVDD grade was not assessed [29]. Of note, based on the CMR of 102 DCM patients, we did not find a statistically sound relation between replacement CF, assessed both qualitatively and quantitatively, and the degree of LVDD. Although, numerically the difference can be observed – half of eLAP vs. 40 % of nLAP patients had LGE.

Only two studies have explored the relationships between a single diastolic parameter, namely E/e' ratio, and ECV; however, none of the studies carried out comprehensive LVDD assessments (as recommended by EACVI) in relation to CF. It was reported by Barison et al., who studied 89 DCM patients with relatively high LVEF (mean LVEF of 41 %), and Azuma et al., who analysed 32 DCM patients with atrial fibrillation, that there existed a significant correlation between E/e' and ECV [30,31]. By way of contrast, we actually found no association between E/e' ratio and ECV, but did uncover one between LAVI and ECV. This is the first observation showing a clear association between LVDD and interstitial fibrosis, expressed as ECV. Although it may seem to be a somewhat obvious observation, this constitutes clear empirical confirmation of the link between interstitial fibrosis and LVDD.

Based on these findings, we may speculate that more-or-less diffuse collagen accumulation in extracellular spaces, expressed as ECV, would appear to be pivotal for the increased stiffness and relaxation impairment of LV, which are "substrates" for LVDD [32]. At the same time, the lack of any clear relation between replacement CF, expressed as LGE, may be explained by the fact that this 'scar tissue' is regional, and as such it may have 'less potential' to produce LVDD [33]. These findings may also have clinical implications since it was shown that interstitial CF may be amenable to experimental 'anti-fibrotic' treatment, which could lead to improvements in LVDD, whereas replacement CF is more of a 'fixed' pathology which, at present, cannot be diminished [34].

What is also interesting, based on our thorough analysis of each LV segment (Fig. 2), it can be concluded that independently of LAP most DCM patients had LGE in intraventricular (IVS) septum, especially in basal segments, as previously reported, while all apical segments were LGE-free [35,36]. However, until now a similar pattern of more advanced LV fibrosis in IVS segments was not confirmed in ECV analysis. Despite this observation, the mean value of all LV segments was similar to the mean ECV of IVS middle segments (29.2 ± 6.0 % vs. 28.8 ± 4.9 %, respectively). Therefore, it can be concluded that a more simplified approach to ECV measurement (as ROI of only middle IVS segments) can be equally effective as the thorough and time-consuming method (mean ECV of all LV segments). However, in contrast to LGE, ECV was also higher in apical segments. In terms of nLAP and eLAP differences, patients with eLAP had significantly more frequent LGE and higher ECV in most LV segments. These findings support the theory that more extensive diffuse (and localised) LV fibrosis affects diastolic (and systolic) function.

4.1. Limitations and strengths

However, the size of the study population is relatively small for the DCM cohort, this is one of the biggest studies analysing cardiac fibrosis in the context of left ventricle diastolic function. Due to the size regression models, especially multivariate models, should be analysed with caution. We include a homogenous group of HF patients, specifically younger individuals (mean age 45 years old) with DCM (with no other comorbidities that could have had a fibrosis-stimulating effect) of a duration that is less than 1.5 years, and with stable HF. These factors enable us to assess the raw relationship between diastolic function and fibrosis in HF. In contrast to those with DCM, the general HF population is much older (70–80 years old), with a collection of different cardiovascular and non-cardiovascular factors (like hypertension, diabetes mellitus, obesity, and lung diseases) that lead to CF. Furthermore, old age itself is a known cause of higher CF and stiffness. Therefore, this homogenous DCM population could be considered the "clear model" of fibrosis in HF.

5. Conclusions

More than two-in-five DCM patients had at least moderate LV diastolic dysfunction and had higher troponin and NT-proBNP levels. However, patients with normal and abnormal diastolic function did not differ in terms of clinical presentation and comorbidities, including NYHA class. There were no differences in LV replacement fibrosis between the groups, but patients with a higher grade of diastolic dysfunction did have more pronounced interstitial fibrosis.

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CRediT authorship contribution statement

Ewa Dziewięcka: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Mateusz Winiarczyk:** Data curation. **Robert Banyś:** Investigation. **Małgorzata Urbańczyk-Zawadzka:** Investigation. **Maciej Krupiński:** Investigation. **Małgorzata Mielnik:** Investigation. **Sylwia Wiśniowska-Śmiałek:** Investigation. **Aleksandra Karabinowska-Małocha:** Data curation. **Agata Leśniak-Sobelga:** Investigation. **Katarzyna Holcman:** Investigation. **Magdalena Kostkiewicz:** Investigation. **Marta Hlawaty:** Investigation. **Piotr Podolec:** . **Jan Robak:** Investigation, Data curation. **Monika Kaciczak:** Data curation. **Filip Baranowski:** Data curation. **Paweł Rubiś:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101426.

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