Open Access Article

Ann. Acad. Med. Siles. (online) 2024; 78: 219–225
eISSN 1734-025X
DOI: 10.18794/aams/189128
www.annales.sum.edu.pl

PRACA ORYGINALNA
ORIGINAL PAPER

Echocardiographic markers of left ventricular hypertrophy and concentric remodeling – limitations in diagnostics of cardiac amyloidosis, Fabry disease and hypertrophic cardiomyopathy

Echokardiograficzne parametry przerostu lewej komory i remodelingu koncentrycznego – ograniczenia w diagnostyce amyloidozy serca, choroby Fabry'ego i kardiomiopatii przerostowej

Judyta Znamirowska, Mateusz Tometczak, Justyna Topa, Patrycja Pastor, Damian Waksmundzki, Adam Grzebinoga, Katarzyna Mizia-Stec

1st Department of Cardiology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

ABSTRACT

INTRODUCTION: Left ventricular hypertrophy (LVH) is a relevant sign associated with an increased risk of sudden death. The causes of LVH including cardiac amyloidosis (CA), Fabry disease (FD), hypertrophic cardiomyopathy (HCM) are associated with an inauspicious prognosis. Transthoracic echocardiography (TTE) remains the first-step baseline diagnostic method.

MATERIAL AND METHODS: A retrospective one-center analysis of 86 patients (pts) with increased left ventricular (LV) wall thickness in TTE was performed. The inclusion criteria were interventricular septum (IVS) above 10 mm in males, 9 mm in females and the final diagnosis of CA, FD or HCM. The study population was divided into three subgroups: CA (13 pts), FD (7 pts), HCM (66 pts). The LV mass index (LVMI), relative wall thickness (RWT) and type of remodeling were analyzed.

RESULTS: Increased LVMI occurred in 90.9% pts with CA, all with FD, 89.5% with HCM.RWT exceeded the normal range among 92.3% pts with CA, 57.1% with FD, 92.4% with HCM. Concentric hypertrophy was diagnosed in 75% pts with CA, 57.1% with FD, 84.2% with HCM and eccentric in 8.3% pts with CA, 42.9% with FD, 5.3% with HCM ($p = 0.01$). An abnormal IVS/PWT index was observed in 23.1% pts with CA, 28.6% with FD, 79.7% with HCM ($p = 0.00001$).

CONCLUSIONS: Although cardiac hypertrophy is a typical sign, it does not occur in all subjects with CA, FD, HCM. More detailed analysis including the form of hypertrophy as well as left atrium remodeling are required to be characterized for specific diseases: CA, FD, HCM. Asymmetrical hypertrophy is more specific for HCM.

KEYWORDS

echocardiography, hypertrophy, remodeling, LVMI, RTW, hypertrophic cardiomyopathy, amyloidosis, Fabry disease

Received: 14.04.2024 **Revised:** 13.05.2024 **Accepted:** 21.05.2024 **Published online:** 20.09.2024

Address for correspondence: lek. Mateusz Tometczak, Klinika Kardiologii I Katedry Kardiologii, Górnośląskie Centrum Medyczne im. prof. Leszka Gieca Śląskiego Uniwersytetu Medycznego w Katowicach, ul. Ziołowa 47, 40-635 Katowice, +48 32 359 88 90, e-mail: mateusztometczak4@gmail.com

Publisher: Medical University of Silesia, Katowice, Poland

STRESZCZENIE

WPROWADZENIE: Przerost lewej komory (*left ventricular hypertrophy* – LVH) jest istotną cechą powiązaną ze wzrostem ryzyka nagłej śmierci sercowej. Typowe przyczyny przerostu obejmujące amyloidozę serca (*cardiac amyloidosis* – CA), chorobę Fabry'ego (*Fabry disease* – FD) oraz kardiomiopatię przerostową (*hypertrophic cardiomyopathy* – HCM) wymagają specyficznego podejścia i rokują niepomyślnie. Echokardiografia przezklatkowa (*transthoracic echocardiography* – TTE) pozostaje wówczas podstawową metodą diagnostyczną.
MATERIAŁ I METODY: Wykonano jednoośrodkową analizę retrospektywną obejmującą 86 pacjentów z przerostem ściany lewej komory (*left ventricular* – LV) stwierdzonym w TTE. Kryteriami włączenia były grubość przegrody międzykomorowej (*interventricular septum* – IVS) powyżej 10 mm u mężczyzn i 9 mm u kobiet oraz potwierdzona diagnoza CA, FD lub HCM. Badana populacja została podzielona na trzy grupy w zależności od końcowej diagnozy: CA (13 pacjentów), FD (7 pacjentów) oraz HCM (66 pacjentów). Analizowano indeks masy lewej komory (LV *mass index* – LVMI), względną grubość ściany lewej komory (*relative wall thickness* – RWT) oraz typ przerostu.
WYNIKI: LVMI powyżej normy obserwowano u 90,9% pacjentów z CA, wszystkich z FD, 89,5% z HCM. RWT powyżej normy obserwowano u 92,3% pacjentów z CA, 57,1% z FD, 92,4% z HCM. Przerost koncentryczny zdiagnozowano u 75% pacjentów z CA, 57,1% z FD, 84,2% z HCM; przerost ekscentryczny zaobserwowano u 8,3% pacjentów z CA, 42,9% z FD, 5,3% z HCM (p = 0,01). IVS/PWT powyżej normy stwierdzono u 23,1% pacjentów z CA, 28,6% z FD, 79,7% z HCM (p = 0,00001).
WNIOSKI: Mimo iż przerost serca jest cechą typową, nie występuje u wszystkich osób z CA, FD, HCM. Do scharakteryzowania konkretnych chorób, jak CA, FD, HCM, wymagana jest dokładniejsza analiza obejmująca typ przerostu oraz remodeling lewego przedsionka. Na podstawie wyników przerost asymetryczny jest bardziej swoisty dla HCM.

SŁOWA KLUCZOWE

echokardiografia, przerost, remodeling, LVMI, RWT, kardiomiopatia przerostowa, amyloidoza, choroba Fabry'ego

INTRODUCTION

Transthoracic echocardiography (TTE) is a key tool in the comprehensive evaluation of left ventricular hypertrophy (LVH) and concentric remodeling, offering invaluable insight into a variety of cardiac diseases, including cardiac amyloidosis (CA), Fabry disease (FD) and hypertrophic cardiomyopathy (HCM) [1]. In CA, TTE plays a key role in detecting myocardial infiltration. Imaging techniques help in the early identification of even small changes, contributing to faster intervention. Furthermore, TTE is a key modality in revealing the complexity of FD, enabling visualization of the characteristic hypertrophy and assessment of disease progression [2]. In HCM, the latest guidelines emphasize the key role of TTE not only in diagnosis, but also during the treatment of the disease. By using advanced imaging techniques, TTE allows a precise assessment of LVH, revealing characteristic features such as asymmetric septal hypertrophy, a hallmark of HCM. Incorporating the latest HCM guidelines into echocardiographic practice increases diagnostic accuracy and facilitates an individualized approach to the treatment of each patient. This interplay between the ongoing changes in guidelines and TTE highlights the invaluable role of cardiac imaging modalities in uncovering the intricate details of LVH and concentric remodeling in the various cardiovascular pathologies that complicate so many diseases. The research involved a group of patients diagnosed in a tertiary, highly specialized cardiology centre in Katowice, which utilized proper methods to diagnose rare illnesses such as CA and FD. Cardiac hypertrophy, which is the baseline of diagnosis, is not in every case connected with HCM. The study found that among 86 patients with suspicion of HCM, 23.3% patients were finally diagnosed with rare phenotypes (CA or FD). The aim of the study was to compare echocardiography parameters of LV remodeling among patients with increased LV wall thickness and the final diagnosis of HCM, CA or FD.

MATERIAL AND METHODS

Study population

A retrospective single-center analysis of 86 patients (pts; mean age 55.4 ± 15.7; 59.5% males) with increased left ventricular (LV) wall thickness in TTE was performed. The patients were hospitalized between 2010–2022 in the 1st Department of Cardiology of the Medical University of Silesia, Katowice, Poland. The inclusion criteria were: 1) thickness of the interventricular septum (IVS) above 10 mm in males and 9 mm in females as the baseline findings [3]; 2) the final diagnosis of CA, FD or HCM. Patients with incomplete echocardiography results were excluded. CA was detected by clinical symptoms and cardiac magnetic resonance imaging (cMRI) or a myocardial biopsy. FD was diagnosed based on the evaluation of an α-galactosidase A by dry blood enzymatic test. HCM was diagnosed by detecting a thickness of the myocardium over 15 mm not caused by overstrain. The study population was divided into three subgroups regarding the final diagnosis: 13 pts with CA (15.1% of all, mean age

62 ± 16.1; 46.2% males), 7 pts with FD (8.1% of all, mean age 40.4 ± 12.5; 57.1% males) and 66 pts with HCM (76.7% of all, mean age 55.6 ± 14.8; 62.5% males). Permission of Research Ethics Committees was not essential because this study was a retrospective assessment.

Echocardiography data

TTE was performed on admission by an experienced cardiologist. The value of the interventricular septum diameter (IVSd), left ventricular internal diastolic diameter (LVIDd), and posterior wall thickness diameter (PWTd) were obtained to calculate the left ventricular mass (LVM) according to the formula: $0.8 \times 1.4 \times [(IVSd + LVIDd + PWTd)^3 - LVIDd^3] + 0.6$ g [4]. However, the LV mass index (LVMI) was determined as LVM/ body surface area (g/m^2). The normal range of the aforementioned parameter was defined as < 115 g/m^2 for men and < 95 g/m^2 for women [4]. Additionally, the left ventricular end-diastolic diameter (LV EDD) was obtained to calculate the relative wall thickness (RWT) using the formula: (IVSd + PWTd)/LV EDDd. The normal range of RWT was considered to be ≤ 0.42 [5,6]. Based on the following echocardiography parameters (LVMI and RWT), the type of LV remodeling was analyzed.

In view of the above:

- concentric hypertrophy was defined as LVMI > N and RWT > N
- eccentric hypertrophy was defined as LVMI > N and RWT < N
- concentric remodeling was defined as LVMI ≤ N and RWT > N
- normal geometry was defined as LVMI ≤ N and RWT < N [7,8].

Additionally, according to the ratio of the interventricular septum to the posterior wall thickness (IVS/PWT) value, it was possible to reveal a symmetrical or asymmetrical form of hypertrophy.

Based on the previous parameter:

- IVS/PWT > 1.3 indicated asymmetrical hypertrophy
- IVS/PWT ≤ 1.3 indicated symmetrical hypertrophy [9].

A further echocardiography parameter that was evaluated was the left atrium area (LA area), for which the normal range was < 20 cm^2 [10].

The correlations of LVMI, RTW, IVS/PWT, LA area parameters and the form of hypertrophy (concentric hypertrophy, eccentric hypertrophy, concentric remodeling and normal geometry as well as asymmetrical and symmetrical hypertrophy) between patients with HCM, CA and FD were assessed.

Statistical analysis

Statistical analysis was performed using Statistica 13.3 software. Quantitative variables were presented in the form of arithmetic mean and standard deviation. Qualitative variables were presented in the form of absolute values and percentages. Intergroup differences for qualitative variables were assessed using the chi-square test, and if the data did not meet its criteria, Fisher's exact test. Intergroup differences were not assessed for quantitative variables. The normality of distributions was assessed using the Shapiro-Wilk test. The criterion of significance was assumed at the level of $p < 0.05$.

RESULTS

Among the study population the mean LVMI was 164.0 g/m^2 ± 54.5, and in 88.0% of patients it was above the normal range. In the subgroup with CA, the mean LVMI was 152.3 g/m^2 ± 46.6 and in 90.9% it was above the upper limit of normal. In the FD population the mean LVMI was 146.6 g/m^2 ± 73.8, and it was above the normal range in 83.3%. In the subgroup with HCM, the mean LVMI was 168.0 g/m^2 ± 54 and it was above the upper limit of normal in 87.9%.

The mean RWT among the whole population was 0.72 ± 0.22 and was not similar among the study subgroups (CA 0.88 ± 0.31, FD 0.53 ± 0.18, HCM 0.71 ± 0.18), whereas the patients with FD had a lower RWT than the other subgroups. RWT above the normal range appeared among 92.3% patients with CA, 57.1% patients with FD and 92.4% patients with HCM. Nevertheless, the FD subgroup had a small standard deviation correlated with a low level.

Concentric hypertrophy evaluated by the comparison of LVMI and RWT was observed in 81.3% of all the patients, and among the FD subgroup it was rarer than the others (CA 81.8%, FD 57.1%, HCM 84.2%). Eccentric hypertrophy was observed in 9.33% of all the patients and it was more common in FD (CA 9.1%, FD 42.9%, HCM 5.3%). Concentric remodeling was not noticed in the FD subgroup (CA 9.1%, FD 0.0%, HCM 10.5%). Previous results were shown in Figure 1. We can observe that among the CA and HCM patients, the vast majority was characterized by concentric hypertrophy, while among the FD subgroup concentric and eccentric hypertrophy were observed in similar numbers.

The mean ratio of IVS to PWT among the whole study population was 1.59 ± 0.5 and it was above the normal range in 66.3%. Compared to HCM, IVS/PWT was lower

in the FD and CA subgroups (CA 1.16 ± 0.25, FD 1.11 ± 0.27, HCM 1.72 ± 0.48). Foregoing results were presented in Figure 2. This showed that asymmetrical hypertrophy was observed in 23.1% of the patients with CA, 16.7% with FD and 79.7% with HCM. The correlation was illustrated in Figure 3. These results show that detected symmetrical hypertrophy can increase the chances of diagnosed CA or FD. That information is consistent with knowledge about the pathophysiology of these diseases.

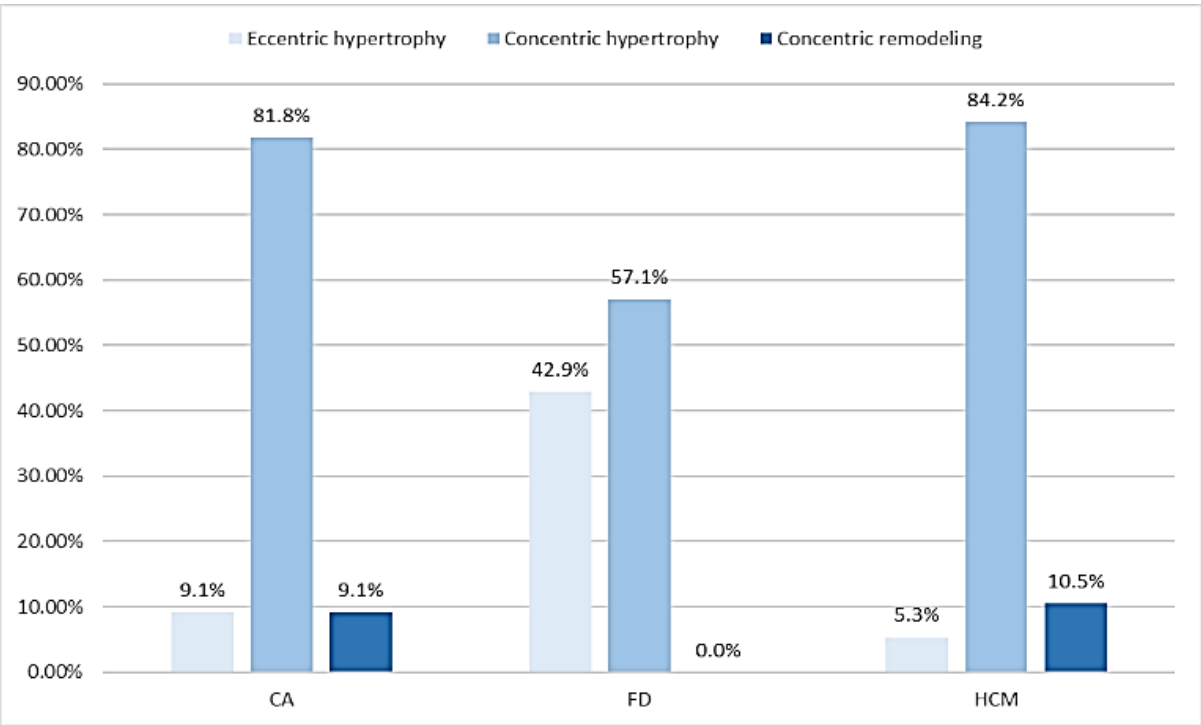

Fig. 1. Patterns of left ventricular geometry in subgroups; CA – cardiac amyloidosis, FD – Fabry disease, HCM – hypertrophic cardiomyopathy.

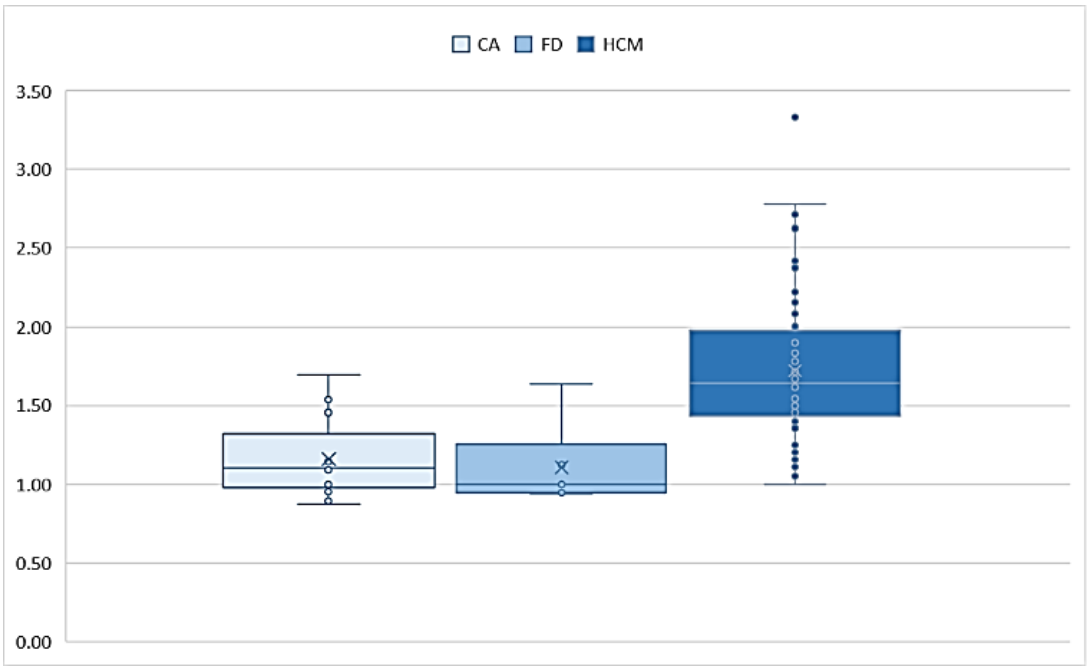

Fig. 2. Values of interventricular septum/posterior wall thickness (IVS/PWT) ratio in subgroups; CA – cardiac amyloidosis, FD – Fabry disease, HCM – hypertrophic cardiomyopathy.

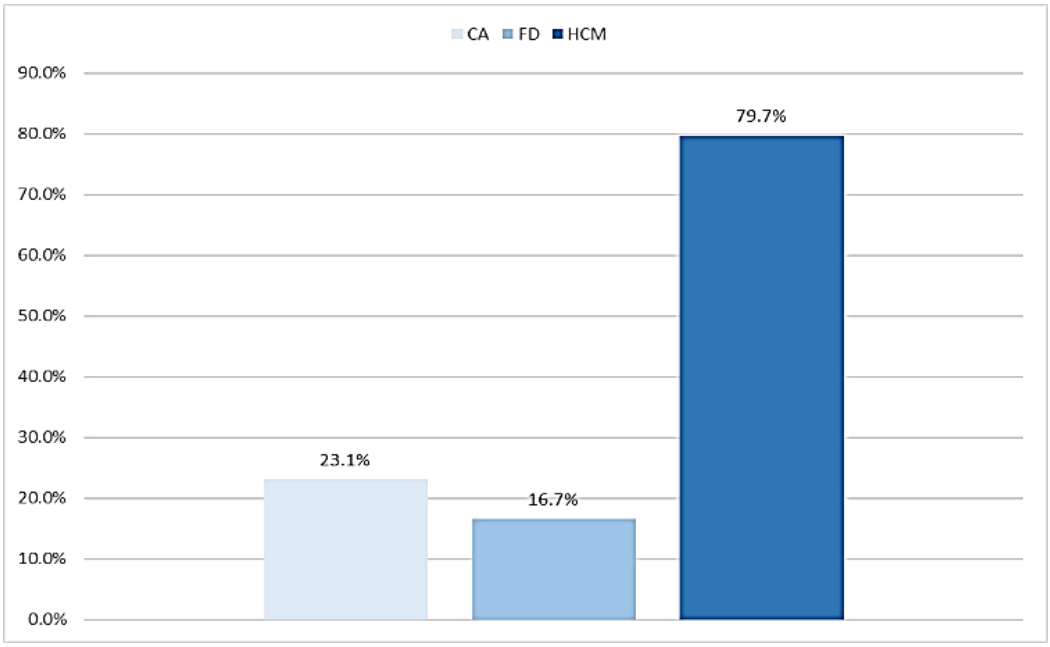

Fig. 3. Interventricular septum/posterior wall thickness (IVS/PWT) ratio in subgroups; CA – cardiac amyloidosis, FD – Fabry disease, HCM – hypertrophic cardiomyopathy.

In our study population the mean LA area amounted to 25.0 $cm^2 \pm 7.5$ and it was above the normal range in 68.8% of all the patients. Among the patients suffering from CA, the mean LA area was 21.1 $cm^2 \pm 4.9$, and it was above the normal range in 63.7% patients. The mean LA area in the subgroup with FD was 21.6 $cm^2 \pm 4.6$ and in the upper limit of normal in 50% of patients. Among the HCM subgroup, the mean LA area amounted to 26.1 $cm^2 \pm 7.8$ and it was above the normal range in 71.7%.

Value of selected and significant echocardiography parameters were performed in Table I.

Table I. Values of echocardiography parameters in subgroups

Parameter	CA	FD	HCM	p
LVMI above normal range n (%)	10 (90.9)	7 (100)	59 (89.5)	p = 1.0 (CA + FD vs HCM)
RWT above normal range n (%)	12 (92.3)	4 (57.1)	60 (92.4)	p = 0.2 (CA + FD vs HCM)
Concentric hypertrophy n (%)	9 (75.0)	4 (57.1)	48 (84.2)	p = 0.5 (CA + FD vs HCM)
Eccentric hypertrophy n (%)	1 (8.3)	3 (42.9)	3 (5.3)	**p = 0.01 (FD vs HCM)** p = 0.1 (FD vs CA)
IVS/PWT above normal range n (%)	3 (23.1)	2 (28.6)	51 (79.7)	**p = 0.00001 (CA + FD vs HCM)**
Left atrium area above normal range n (%)	7 (63.7)	3 (50.0)	43 (71.1)	p = 0.4 (CA + FD vs HCM)

CA – cardiac amyloidosis; FD – Fabry disease; HCM – hypertrophic cardiomyopathy; LVMI – left ventricular mass index; RWT – relative wall thickness; IVS/PWT – interventricular septum/posterior wall thickness ratio.

DISCUSSION

The LVH phenotype in echocardiography is a frequent finding in daily clinical practice. Moreover, echocardiographic markers play an important role in the non-invasive detection of its underlying causes, among others in HCM, CA, and FD [2]. Differentiation of the etiology of LVH is important so that appropriate treatment can be started [11]. Although the clinical context is key, there are situations where echocardiographic features, as one of the first tests performed, may raise suspicion of specific diseases or narrow the differential diagnosis [12]. The early detection of FD is especially important because the availability of the specific treatment of enzyme replacement therapy may alter the outcome [11,13,14].

HCM is a genetic cardiomyopathy, most often caused by mutations in genes encoding cardiac sarcomeric proteins [15]. Moreover, it is also the most common non-ischemic cardiomyopathy [16]. The classic LVH pattern in HCM is asymmetrical thickening of the IVS [17]. The study by Patil and Wiegers [15] reports that

asymmetric septal hypertrophy (ASH) occurs in approximately 75% of cases. Analogously in our work, an asymmetrical pattern of hypertrophy was observed in 79.7% of the patients with HCM. However, it should be underlined that this is not a pathognomonic pattern for HCM. It may also occur, although less frequently, in infiltrative cardiomyopathies [12].

CA is a disorder that results from extracellular amyloid deposits in the heart [11]. In the literature, echocardiographic features associated with CA include concentric LVH, right ventricular hypertrophy, dilated atria, and pericardial effusion [2,18,19]. Furthermore, LVH is the most common echocardiographic finding in patients with CA [1,18]. This is presented in our work, where concentric hypertrophy was described in 81.8% of patients and the mean LA area was above the normal range in 63.3% of patients. Nevertheless, clinicians should be aware that other morphological patterns in echocardiography, although less common, also occur. CA can be difficult to differentiate from HCM patients [12,16]. Echocardiographic similarities between these two diseases may include an increased LV wall thickness, atrial enlargement, and diastolic dysfunction [12]. Similar to this report, in our study the echocardiographic parameters and ventricular remodeling patterns are very close, except for the fact that asymmetric hypertrophy is more characteristic of HCM.

TTE is often the first-line imaging method for the evaluation of cardiac abnormalities in FD [17]. The literature states that the most common ventricular remodeling pattern in FD is concentric hypertrophy. Concentric remodeling, asymmetric hypertrophy, and eccentric hypertrophy are occasionally observed in these studies [13,14,17]. Nonetheless, our research shows that among the FD subgroup, concentric and eccentric hypertrophy patterns were observed in similar amounts. This presents a way to differentiate FD from HCM, where eccentric hypertrophy was much less common in our work. However, when analyzing this result, the small size of the FD subgroup should be taken into account. We did not observe in this subgroup a concentric remodeling pattern. FD is difficult to diagnose based on echocardiography alone, thus other clinical features should be taken into account [20].

The literature agrees that no single echocardiography parameter can perfectly differentiate HCM, FD and CA [12,15,16]. Nevertheless, a combination of symptoms, history, electrocardiography findings, and echocardiographic results can help narrow differential diagnosis [12]. The limitation is that the issue concerns relatively rare diseases, which results in a small number of studies, but the possibility of effective treatment should increase interest. The topic requires further research [12].

The main limitation of the study is the small number of patients in the population, especially patients diagnosed with CA and FD, because these diseases are extremely rare.

An advantage of the research is expanded diagnostics beyond the hypertrophy phenotype and complete examinations for CA and FD such as cMRI, the dry blood spot test and myocardial biopsy.

CONCLUSIONS

Although cardiac hypertrophy is a typical sign, it does not occur in all subjects with HCM, CA, FD. More detailed analysis including the form of hypertrophy (concentric, eccentric, symmetrical, asymmetrical) as well as LA remodeling are more characteristic for specific diseases such as HCM, CA, FD. Based on the results, asymmetrical hypertrophy is more specific for HCM than for CA and FD.

Author's contribution

Study design – K. Mizia-Stec
Data collection – M. Tometczak, J. Znamirowska, J. Topa, P. Pastor, D. Waksmundzki, A. Grzebinoga
Data interpretation – M. Tometczak, J. Znamirowska, K. Mizia-Stec
Statistical analysis – J. Topa
Manuscript preparation – M. Tometczak, J. Znamirowska, J. Topa, P. Pastor, D. Waksmundzki, A. Grzebinoga
Literature research – J. Topa, P. Pastor, D. Waksmundzki, A. Grzebinoga

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