

Influence of hereditary haemochromatosis on left ventricular wall thickness: does iron overload exacerbate cardiac hypertrophy?

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Background: The left ventricular (LV) hypertrophy increases the risk of heart failure. Hypertension and infiltrative cardiomyopathies are the well-known reasons of LV hypertrophy. The growing interest of scientists in this issue affects hereditary haemochromatosis (HH), which is characterised by the excess deposition of iron mostly due to HFE gene mutation. The aim of our study was to investigate the possible influence of HH on LV parameters in patients with early-diagnosed (early HH) and long-lasting and long-treated (old HH) disease.

Materials and methods: Thirty nine early HH and 19 old HH patients were prospectively enrolled in the study; age- and sex-matched healthy volunteers constituted the appropriate control groups. All participants had echocardiography performed (including three-dimension volume and mass analysis); the iron turnover parameters were measured at the time of enrolment in every HH patients.

Results: Echocardiographic parameters regarding to left atrium (LA), LV thickness, mass and long axis length were significantly higher, whereas LV ejection fraction was lower in early HH in comparison to healthy persons. In old HH patients the differences were similar to those mentioned before, except LV ejection fraction. The presence of hypertension in both HH groups did not influence echo parameters, as well as diabetes in old HH. The strongest correlation in all HH group was found between the time from HH diagnosis and LA, LV thickness and volumes parameters, but the correlations between iron turnover and echo parameters were non-existent.

Conclusions: Hereditary haemochromatosis, not only long-lasting, but also early-diagnosed, could lead to exacerbation of LV wall thickness and cardiac hypertrophy. This effect is not simply connected with hypertension and diabetes that are frequent additional diseases in these patients, but with the time from HH diagnosis. (*Folia Morphol* 2019; 78, 4: 746–753)

Key words: hereditary haemochromatosis, echocardiography, left ventricular hypertrophy, heart siderosis, heart morphology, diabetes mellitus, arterial hypertension

INTRODUCTION

The left ventricular (LV) hypertrophy (LVH) is a well-known clinical and morphological parameter that is considered to be the important risk factor for heart failure [5, 8]. It occurs typically in response to the haemodynamic overload in some physiological and pathological conditions, and hypertension is the most important reason for LVH development [18]. The infiltrative cardiomyopathies are the next well-known reason of LVH. This is a diverse group of cardiac diseases characterised by the deposition of abnormal substances within the heart tissue that causes the ventricular walls to develop either diastolic or, less common, systolic dysfunction. Recently the growing interest of scientists in this issue affects hereditary haemochromatosis (HH), which is characterised by the excess deposition of iron mostly due to HFE gene mutation [1, 12, 14]. Dysfunction of molecules that control iron homeostasis leads to excessive iron absorption in the duodenum and upper section of the small intestine, as well as its maldistribution. As there is no regulatory mechanism for iron excretion from the human body, iron is deposited in a variety of tissues and organs (liver, pancreas, skin, joints, heart) over the course of the disease [1, 11, 16]. Bioactive iron ions produce oxidative stress that destroys involved tissues [6, 13, 15]. Cardiomyocytes, due to intense iron intake, are very susceptible to this type of damage [17]. Symptoms of HH are nonspecific and typically absent in the early stages, therefore a high degree of clinical suspicion is key to making the diagnosis.

Echocardiography, especially with the use of novel three-dimension (3D) techniques, is one of the most important tools for revealing cardiac abnormalities; LVH is one of the most noticeable alterations which can be detected by echocardiography and is very common complication of HH. Therefore, the aim of our study was to investigate the possible influence of HH on LV parameters in different groups of HH patients: with early-diagnosed disease and with long-lasting and long-treated pathology.

MATERIALS AND METHODS

Study population

From November 2014 to November 2018, we prospectively enrolled the patients with newly diagnosed HH (i.e. within 3 months of the initial clinical diagnosis, before receiving HH-specific treatment) [*early HH*] and the patients with HH treated at least 5 years [*old HH*]. HH was initially diagnosed in specialist

clinic based on clinical characteristics, abnormal iron turnover parameters and the presence of HFE gene mutations [4]. Healthy age- and sex-matched volunteers constituted two control groups: 26 to *early HH* and 24 to *old HH* patients. All participants underwent classic echocardiography imaging. The protocol of the study was approved by the Local Ethics Committee at the Medical University of Gdansk, and written informed consent was obtained from all participants. The exclusion criteria were as follows: age < 18 years; history of any cardiological diagnosis (apart from the hypertension). In all HH patients, the levels of iron, serum ferritin, transferrin saturation, haemoglobin, glucose and transaminases level were measured at the time of enrolment.

Echocardiography

Echocardiography was performed in every person enrolled into the study. The patients were examined in the left lateral decubitus position using a GE VIVID E9 ultrasound system (GE Ultrasound, Horten, Norway) equipped with phased-array transducer (M5S). During the same echocardiographic examination 3D datasets were acquired in apical view using a commercially available matrix-array 3D transducer (4V).

Standard echocardiographic parameters were obtained according to the principles described in recommendations [9]. Data acquisitions were obtained from parasternal long- and short-axis views and the three standard apical views. For each view, three consecutive cardiac cycles were recorded during quiet respiration. Grayscale recordings were optimised for LV evaluation at a frame rate of 50–80 frames/s and only persons with these parameters were included into the further analyses. All echocardiograms were stored digitally and further offline analysis was performed using commercial workstation EchoPAC (v201, GE Healthcare Horten, Norway).

Analysis of 2D parameters. Left atrium (LA) diameters (LADs), indexed LA area (LAA index) and indexed LA volume (LAV index), LV end-diastolic diameters (LVEDD), LV end-systolic diameter (LVESD), intraventricular septal (IVS) and posterior wall (PW) thickness were measured in parasternal view. The relative wall thickness (RWT) was calculated as the sum of anteroseptal and posterior wall thickness divided by the LV end-diastolic dimension. LV diastolic longitudinal length was measured as the distance between the mitral annulus and the apex in end-diastole averaged from the 4-, 2- and 3-chamber apical views.

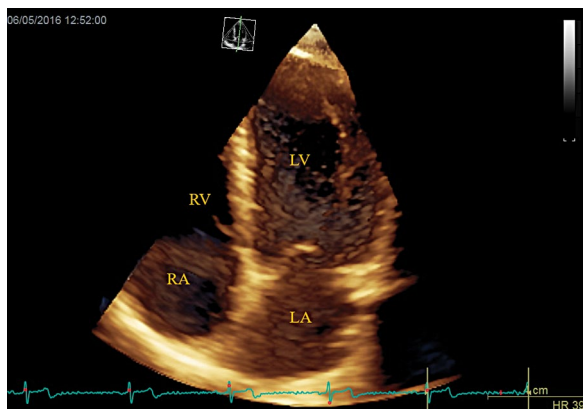


Figure 1. The example of three-dimensional, full-volume echo view for volume, mass and ejection fraction assessment; LA — left atrium; LV — left ventricle; RA — right atrium; RV — right ventricle.

Analysis of 3D parameters. After manual alignment of the three apical views and the short-axis view, points were placed in the mitral annular plane and at the apex, in end-diastole and end-systole. Endocardial and epicardial border were automatically detected by the software, but manually corrected, if necessary. End-diastolic (LVEDV), end-systolic (LVESV) volumes, 3D LV ejection fraction (LVEF) and LV mass (LVM) were measured (Fig. 1).

Statistical analysis

Continuous data are presented as the median (25th–75th percentiles), while categorical data are expressed as proportions. We performed the Shapiro-Wilk test to determine whether our data were normally distributed. The majority of the analysed parameters did not have normal data distributions, even after logarithmic data transformation; thus, we selected appropriate statistical analysis methods based on non-parametric tests. Comparisons between groups were performed with the Mann-Whitney U

test for continuous variables and Pearson's chi-square test for categorical variables, when appropriate. The correlations between laboratory parameters and echo parameters were evaluated using Spearman's correlation coefficient. P-values less than 0.05 were considered significant. The statistical analysis was conducted with STATISTICA 9.0 (StatSoft, Tulsa OK, USA) and R 2.15.2.

RESULTS

Thirty nine patients constituted the *early HH* group and 19 patients the *old HH* group, age- and sex-matched healthy volunteers constituted the appropriate control groups (due to the fact that the *old HH* patients were older than *early HH* patients, there were two respective control groups in our study). The genetic characteristics of the *early HH* patients were as follows: 28 patients had the C282Y/C282Y genotype, 7 — C282Y/H63D genotype, 3 — H63D/H63D genotype, and 1 — C282Y/wt genotype, whereas the *old HH* patients were C282Y/C282Y, except 2 patients — C282Y/H63D.

Table 1 shows biochemical results of the patients at the time of enrolment. *Early HH* had significantly higher ferritin level, whereas the glycaemia level was higher in *old HH* group.

In comparison between *early HH* group and the healthy persons there were a number of differences regarding to: LA parameters (LADs and LAV index), LV thickness (IVS, PW and RWT) and mass (LVM index), as well as to LV long axis length, which appeared to be significantly higher in *early HH* patients. Figures 2A–C demonstrate the example of 2D echo views in *early HH* patients, whereas Figures 3A–C — the 2D echogram of the healthy person. 3D echocardiography showed bigger LVESV and lower LVEF in *early HH* patients (Table 2). It should be noted that all mentioned echo parameters were within the normal range.

Table 1. HH patients' laboratory characteristics at enrolment

	<i>Early HH</i> (n = 39)	<i>Old HH</i> (n = 19)	P
Iron [μg/dL]	170 (148–215)	159 (130.5–214)	0.233
Ferritin [ng/mL]	421.5 (271–860)	192 (82–223)	< 0.001
TSAT [%]	79 (60.5–91.8)	71 (65.8–81.5)	0.228
Haemoglobin [mg/dL]	15.1 (14–16)	15.1 (14.2–16)	0.474
Glycaemia [mg%]	94 (87–98)	103 (97–104)	< 0.009
ASPAT [U/L]	24 (18–38)	24 (20.5–37)	0.433
ALAT [U/L]	35 (24–64)	26 (21–44)	0.209

Data are presented as the median (25th–75th percentile); TSAT — transferrin saturation; ASPAT—aspartate transaminase; ALAT — alanine transaminase

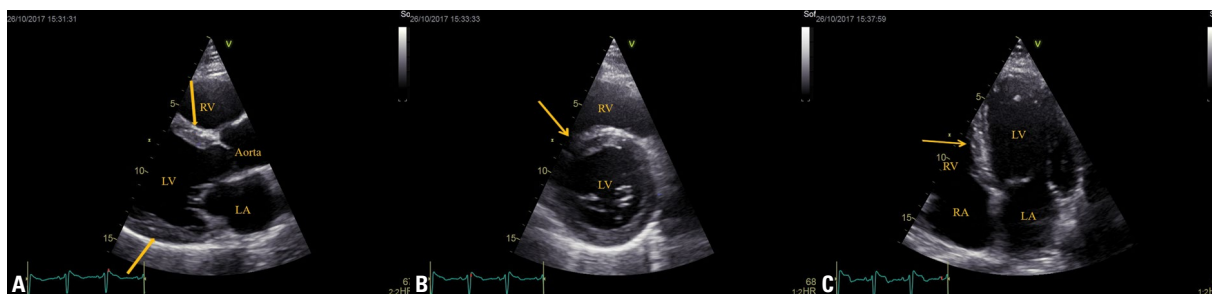


Figure 2. **A.** The example of parasternal long-axis view in *early HH* patient (IVS 12 mm, PW 12 mm). Arrows point the locations where the measures were taken; **B.** The example of parasternal short-axis view in *early HH* patient (IVS 12 mm). Arrow points the location where the measure was taken; **C.** The example apical 4-chamber view in *early HH* patient. Arrow points the location where the measure was taken; IVS — intraventricular septum; LA — left atrium; LV — left ventricle; RA — right atrium; RV — right ventricle; PW — posterior wall.

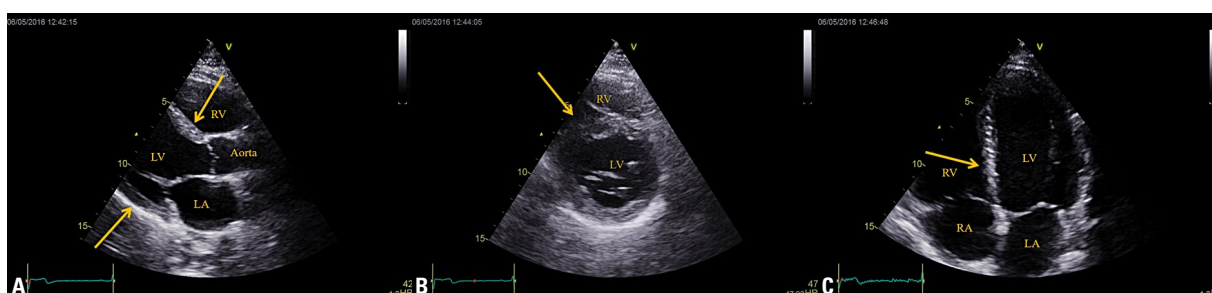


Figure 3. **A.** The example of parasternal long-axis view in healthy person (IVS 9 mm, PW 9 mm). Arrows point the locations where the measures were taken; **B.** The example of parasternal short-axis view in healthy person (IVS 10 mm). Arrow points the location where the measure was taken; **C.** The example apical 4-chamber view in healthy person. Arrow points the location where the measure was taken; RA — right atrium; RV — right ventricle; LA — left atrium; LV — left ventricle; IVS — intraventricular septum; PW — posterior wall.

Table 2. Comparison of echocardiographic parameters between *early HH* and healthy groups

	Healthy volunteers (n = 26)	Early HH (n = 39)	P
Age [years]	44 (35–53)	38 (31–53)	0.199
LADs [mm]	37 (34–39)	42 (36–45)	< 0.003
LAA index [cm ² /BSA]	9.0 (8.2–9.85)	9.1 (7.8–10.1)	0.418
LAV index [mL/BSA]	21 (18–24)	27 (23–34)	< 0.001
IVS [mm]	9 (7–9)	10 (8–11)	< 0.005
PW [mm]	8 (7–9)	9 (7–10)	< 0.043
RWT	0.37 (0.33–0.41)	0.42 (0.38–0.46)	< 0.001
LVEDD [mm]	44 (42–47)	45 (43–48)	0.111
LVESD [mm]	28 (26–29)	28 (25–29)	0.487
LVM index [g/BSA]	65 (54–71)	67 (56–92)	< 0.045
LV long axis length [mm]	74 (69–79)	78 (74–81)	< 0.033
LVEDV [mL]	105 (89–124)	118 (97–133)	0.089
LVESV [mL]	38 (33–46)	50 (39–56)	< 0.005
LVEF [%]	63 (61–65)	60 (54–61)	< 0.001

Data are presented as the median (25th–75th percentile); BSA — body surface area; LV — left ventricular; LADs — left atrial diameters; LAA index — left atrium area/BSA; LAV index — left atrium volume/BSA; IVS — intraventricular septum; PW — posterior wall; RWT — relative wall thickness; LVEDD — LV end-diastolic diameter; LVESD — LV end-systolic diameter; LVM index — LV mass/BSA; LVEDV — LV end-diastolic volume; LVESV — LV end-systolic volume; LVEF — LV ejection fraction

In *old HH* patients the differences were very similar to those mentioned before; there were differences

in the LA parameters (LADs, LAA index, LAV index), LV thickness (IVS, PW, RWT, LVM index) and LV long

Table 3. Comparison of echocardiographic parameters between *old HH* and healthy groups

	Healthy volunteers (n = 24)	Old HH (n = 19)	P
Age [years]	49 (43–62)	53 (48–65)	0.183
LADs [mm]	38 (34–39)	42 (38–43)	< 0.004
LAA index [cm ² /BSA]	9.2 (8.0–9.9)	10.5 (8.2–12.0)	0.082
LAV index [mL/BSA]	22 (19–28)	35 (32–39)	< 0.001
IVS [mm]	9 (7–10)	12 (10–12)	< 0.001
PW [mm]	8 (7–10)	11 (9–12)	< 0.001
RWT	0.38 (0.34–0.43)	0.44 (0.39–0.49)	< 0.019
LVEDD [mm]	45 (42–47)	46 (45–49)	0.062
LVESD [mm]	28 (26–30)	29 (25–34)	0.215
LVM index [g/BSA]	68 (55–73)	93 (77–102)	< 0.001
LV long axis length [mm]	72 (66–77)	81 (73–82)	< 0.004
LVEDV [mL]	96 (86–120)	93 (79–111)	0.225
LVESV [mL]	36 (33–43)	37 (28–45)	0.476
LVEF [%]	63 (61–65)	61 (55–65)	0.093

Data are presented as the median (25th–75th percentile); BSA — body surface area; LV — left ventricular; LADs — left atrial diameters; LAA index — left atrium area/BSA; LAV index — left atrium volume/BSA; IVS — intraventricular septum; PW — posterior wall; RWT — relative wall thickness; LVEDD — LV end-diastolic diameter; LVESD — LV end-systolic diameter; LVM index — LV mass/BSA; LVEDV — LV end-diastolic volume; LVESV — LV end-systolic volume; LVEF — LV ejection fraction

Table 4. Comparison of echocardiographic parameters between HH patients with and without arterial hypertension

	Early HH without hypertension (n = 29)	Early HH with hypertension (n = 10)	P	Old HH without hypertension (n = 7)	Old HH with hypertension (n = 12)	P
Age [years]	33 (30–44)	55 (53–61)	< 0.001	50 (42–55)	59 (53–65)	0.102
LADs [mm]	37 (34–42)	44 (42–45)	< 0.008	35 (34–42)	43 (42–45)	< 0.018
LAA index [cm ² /BSA]	8.7 (7.8–9.8)	9.6 (8.1–10.5)	0.145	9.2 (8.1–10.7)	11.3 (9.1–12.7)	0.123
LAV index [mL/BSA]	24 (22–30)	34 (32–38)	0.021	32 (27–36)	35 (34–42)	0.080
IVS [mm]	10 (8–11)	11 (8–12)	0.231	12 (10–13)	12 (10–12)	0.481
PW [mm]	9 (7–10)	10 (8–11)	0.151	10 (9–11)	11 (9–12)	0.322
RWT	0.42 (0.38–0.45)	0.42 (0.37–0.49)	0.417	0.4 (0.38–0.45)	0.47 (0.4–0.51)	0.170
LVEDD [mm]	46 (43–48)	45 (42–49)	0.436	47 (46–50)	45 (43–48)	0.146
LVESD [mm]	28 (26–30)	27 (25–29)	0.214	28 (25–32)	29 (26–34)	0.428
LVM index [g/BSA]	66 (56–80)	90 (56–100)	0.148	95 (93–103)	84 (72–100)	0.149
LV long axis [mm]	78 (74–83)	77 (74–81)	0.232	82 (82–85)	77 (72–81)	< 0.046
LVEDV [mL]	118 (97–133)	123 (104–134)	0.458	110 (97–113)	84 (76–99)	0.192
LVESV [mL]	51 (39–56)	50 (42–56)	0.442	39 (28–52)	37 (30–41)	0.435
LVEF [%]	57 (54–62)	60 (59–60.3)	0.299	62 (53–67)	60 (57–64)	0.414

Data are presented as the median (25th–75th percentile); BSA — body surface area; LV — left ventricular; LADs — left atrial diameters; LAA index — left atrium area/BSA; LAV index — left atrium volume/BSA; IVS — intraventricular septum; PW — posterior wall; RWT — relative wall thickness; LVEDD — LV end-diastolic diameter; LVESD — LV end-systolic diameter; LVM index — LV mass/BSA; LVEDV — LV end-diastolic volume; LVESV — LV end-systolic volume; LVEF — LV ejection fraction

axis length, but the differences in LVEDV, LVESV and LVEF were not statistically significant (Table 3).

When conducting the separate analysis for *early HH* and *old HH* with and without arterial hypertension we did not confirm the differences in LV thickness parameters (IVS, PW, RWT); LVM index was similar in compared patients as well (Table 4).

Among 19 *old HH* patients, 6 had diabetes. Comparing the echocardiographic parameters between those with and without diabetes, we did not confirm the differences in LV thickness parameters (IVS, PW, RWT); LVM index was similar in compared patients as well (Table 5). Among early HH patients, only 2 had diabetes; therefore, the statistical analysis was not appropriate for this group.

Table 5. Comparison of echocardiographic parameters between old HH patients with and without diabetes mellitus

	<i>Old HH without diabetes (n = 13*)</i>	<i>Old HH with diabetes (n = 6*)</i>	P
Age [years]	51 (44–57)	64.5 (58–66.5)	< 0.035
LADs [mm]	42 (35–43)	44 (42–45)	< 0.030
LAA index [cm ² /BSA]	10.5 (8.3–11.5)	11.5 (8.6–13.5)	0.192
LAV index [ml/BSA]	35 (31–38)	36 (34–43)	0.174
IVS [mm]	11 (10–12)	12 (11–14)	0.100
PW [mm]	10 (9–11)	12 (11–12)	0.090
RWT	0.42 (0.36–0.47)	0.49 (0.45–0.52)	0.061
LVEDD [mm]	47 (45–48)	46 (42–48)	0.318
LVESD [mm]	29 (25–31)	31 (25–34)	0.444
LVM index [g/BSA]	93 (75–96)	95 (85–117)	0.227
LV long axis length [mm]	82 (74–82)	79 (73–84)	0.462
LVEDV [mL]	101 (88–112)	80 (75–83)	0.128
LVESV [mL]	40 (34–49)	29 (26–37)	0.167
LVEF [%]	60 (54–62)	65 (58–66)	0.182

Data are presented as the median (25th–75th percentile); BSA — body surface area; LV — left ventricular; LADs — left atrial diameters; LAA index — left atrium area/BSA; LAV index — left atrium volume/BSA; IVS — intraventricular septum; PW — posterior wall; RWT — relative wall thickness; LVEDD — LV end-diastolic diameter; LVESD — LV end-systolic diameter; LVM index — LV mass/BSA; LVEDV — LV end-diastolic volume; LVESV — LV end-systolic volume; LVEF — LV ejection fraction

Table 6. Correlations between iron turnover and echo parameters in all HH patients

	Iron		Ferritin		Transferrin saturation		Time from diagnosis	
	r	p	r	p	r	p	r	p
LADs [mm]	0.110	0.414	0.058	0.669	0.161	0.239	0.189	0.160
LAA index [cm ² /BSA]	–0.005	0.974	–0.138	0.323	–0.134	0.345	0.400	< 0.003
LAV index [mL/BSA]	–0.017	0.903	–0.193	0.167	–0.052	0.714	0.395	< 0.003
IVS [mm]	–0.077	0.569	0.067	0.626	–0.116	0.398	0.522	< 0.001
PW [mm]	0.020	0.880	–0.035	0.795	–0.118	0.390	0.496	< 0.001
RWT	0.027	0.843	0.035	0.800	–0.048	0.727	0.259	0.051
LVEDD [mm]	0.044	0.744	0.201	0.138	0.103	0.453	0.195	0.125
LVESD [mm]	–0.036	0.790	–0.081	0.553	–0.044	0.752	0.211	0.115
LVM index [g/BSA]	–0.031	0.818	0.075	0.581	–0.037	0.789	0.530	< 0.001
LV long axis [mm]	0.101	0.467	0.201	0.149	–0.213	0.129	0.055	0.695
LVEDV [mL]	0.152	0.659	0.117	0.424	–0.144	0.330	–0.337	< 0.018
LVESV [mL]	0.065	0.659	0.117	0.424	–0.144	0.330	–0.337	< 0.018
LVEF [%]	0.068	0.640	0.008	0.957	–0.041	0.780	0.219	0.130

BSA — body surface area; LV — left ventricular; LADs — left atrial diameters; LAA index — left atrium area/BSA; LAV index — left atrium volume/BSA; IVS — intraventricular septum; PW — posterior wall; RWT — relative wall thickness; LVEDD — LV end-diastolic diameter; LVESD — LV end-systolic diameter; LVM index — LV mass/BSA; LVEDV — LV end-diastolic volume; LVESV — LV end-systolic volume; LVEF — LV ejection fraction

The strongest correlations in all HH group were found between the time from HH diagnosis and LA parameters (LADs, LAA index, LAV index), LV thickness parameters (IVS, PW, LVM index) and LV volumes (LVEDV and LVESV), whereas there were no correlations between iron turnover and echo parameters (Table 6).

DISCUSSION

The most important finding of our study is the observation that in patients with HH the parameters regarding to LV wall thickness were significantly worse than in age-matched healthy persons. Those differences were independent of hypertension and diabetes, but correlated with the time from initial HH

diagnosis. The additional novelty of our study can be found in the demonstration that not only long-lasting HH leads to LVH, but even early-diagnosed HH is characterised by higher LV wall thickness parameters in comparison to age- and sex-matched healthy volunteers. It is worth to note, that *early HH* subgroup of patients was established in short time (within 3 months) after initial diagnosis, before specific HH treatment. However, despite the lack of any cardiological symptoms and the absence of cardiological history, they presented worse LV thickness parameters. Myocardial iron loading of the heart is well known as a possible complication in late stages of HH in terms of both diastolic and systolic function [6], but we revealed some differences in heart morphology even in early-diagnosed, not treated HH, where LV thickness parameters were lower than in the *old HH* patients, but were prominent and significantly worse than in control group.

When evaluating the overall results of this study, it should be noted, that echocardiographic assessment of HH patients revealed some other differences in comparison with healthy volunteers. Besides augmentation of rudimentary parameters (IVS, PW, RWT) we detected increased LA parameters, which is known as a typical consequence of LVH and diastolic dysfunction. In addition, LV long axis length, volume and mass were significantly worse in HH patients in comparison with controls; these differences have been noted in both HH groups. All of this undoubtedly suggests that we may deal with haemochromatosis-induced cardiomyopathy rather, than with simple LV thickening. This statement, however, needs to be confirmed in further studies with larger groups of HH patients and possible follow-up period. According to methodology of our study, it should be underlined, that LV volume and mass were quantified with the use of 3D echocardiography — the technique, which is considered to be comparable with magnetic resonance in relation to abovementioned parameters [2, 7].

Finally, it is important to refer to common HH comorbidities: hypertension and diabetes. LVH is an important marker of hypertension [10, 19, 20] and diabetes-mediated organ damage [3]. That is why we ruled out the possible impact of these pathologies on LV thickness, demonstrating the lack of significant differences (Tables 4, 5).

We are well aware of potential limitations of our study. This was a small, single-centre study, and therefore its results need to be confirmed in a larger group of patients.

CONCLUSIONS

Hereditary haemochromatosis, not only long-lasting, but also early-diagnosed, could lead to exacerbation of LV wall thickness and cardiac hypertrophy. This effect is not simply connected with hypertension and diabetes that are frequent additional diseases in these patients, but with the time from HH diagnosis.

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