

Does the age of patients with hereditary hemochromatosis at the moment of their first diagnosis have an additional effect on the standard echocardiographic parameters?

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Abstract

Background: Hereditary haemochromatosis (HH) is an inherited disease in which gene mutation leads to excessive iron absorption and accumulation in different organs, including the heart, which causes damage. Whether the age of patients with HH at the moment of their first diagnosis has an additional effect on the standard echocardiographic parameters was the aim of the study. **Material and methods:** We prospectively enrolled 20 HH patients, and 20 healthy age- and sex-matched volunteers. Analysis of standard echocardiographic parameters was performed and compared in subgroups of ≥ 50 and < 50 years old (yo). **Results:** Comparing HH patients with healthy volunteers in ≥ 50 yo subgroup, significant differences were found in parameters regarding diastolic function (IVS thickness, LVM index, Em, E/Em, PV S/D, LAA index and LAV index). In the < 50 yo subgroup we did not find the abovementioned differences, however LVEF appeared to be lower in the HH patients. **Conclusions:** Despite the lack of clinical symptoms of cardiovascular disease and the lack of deviations in the standard echocardiographic examination, there were a number of differences regarding LV diastolic function parameters in HH patients ≥ 50 yo, whereas differences regarding LV systolic function were more prominent in HH patients < 50 yo when compared with healthy subjects.

Keywords: age • echocardiography • hereditary hemochromatosis

Citation

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Introduction

Hereditary haemochromatosis (HH) is one of the most common inherited metabolic diseases among Caucasians. In over 80% of cases, it is associated with homozygous mutations in the C282Y HFE gene and occasionally with mutations in other genes, whose products are involved in the regulation of iron turnover in the human body [1]. Dysfunction of molecules that control iron homeostasis leads to excessive iron absorption. As there is no regulatory mechanism for iron excretion from the human body, iron is deposited in many organs. Bioactive iron ions produce oxidative stress that destroys involved tissues. Cardiomyocytes, due to intense iron intake, are very susceptible to this oxidative stress-induced damage. The late symptom of the disease is congestive heart failure, which is responsible for approximately 1/3 of deaths from the natural course of hemochromatosis [1]. Genetic testing allows diagnosis at an early stage and the start of treatment early enough to inhibit the structural changes in organs, including the heart [1-2]. Literature describes a phenomenon of late heart damage in terms of both diastolic and systolic function in HH [2-4]. However, from a clinical point of view the group of patients with newly diagnosed HH, who have not presented any cardiac symptoms, seems to be very interesting, firstly – because of limited literature considering this group and secondly – because of possibility of early treatment introduction in the preclinical stage of the disease [5].

Aim

The aim of this study, is to assess whether the age of patients at the moment of HH diagnosis has an additional effect on the morphology and function of the heart analysed in standard echocardiography.

Materials and methods

Study group

We enrolled 20 patients who were diagnosed with HH <3 months ago but before the start of any HH-specific treatment. All patients had a clinical diagnosis of HH made based on the following criteria: clinical characteristics of the patients, abnormal iron turnover parameters and the presence of HFE gene mutation [6]. Additional criteria included: age ≥ 18 years, the lack of clinical symptoms of any cardiovascular diseases, and the lack of medical history of heart diseases, high blood pressure and diabetes. Twenty healthy age- and sex-matched volunteers constituted the control group.

Laboratory analysis

At the time of first visit, all HH patients had blood drawn and their levels of serum iron and ferritin level,

transferrin saturation (TSAT), hemoglobin and glucose levels were measured.

Conventional Echocardiography

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). Standard echocardiographic parameters were obtained according to the principles described in the ASE/EACVI recommendations [7]. 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 optimized for LV evaluation at a rate of 50-80 frames/s and only patients with these parameters were included in the further analyses. All echocardiograms were stored digitally and further offline analysis was performed using an EchoPAC workstation (v201, GE Healthcare Horten, Norway).

Analysis of 2D and Doppler parameters

Left atrial diameters (LADs), LV end-diastolic diameters (LVEDD), LV end-systolic diameter (LVESD), interventricular septal (IVS) and posterior wall (PW) thickness were measured in the 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. LVMI was calculated according to the ASE/EACVI recommendations [7-8]. The LV volumes and LVEF were measured using the biplane Simpson's rule. The mitral inflow velocity was obtained from the apical 4-chamber view by placing a pulsed-wave Doppler sample volume between mitral leaflet tips during diastole. The peak early (E) and late (A) transmitral flow velocities and deceleration time of E velocity (DT) were measured; the ratio of early-to-late peak velocities (E/A) was calculated. Tissue doppler imaging (TDI) was performed to measure mitral annulus excursion: pulsed wave sample volume was placed at the lateral and septal corner of the mitral valve annulus, early diastolic (Em) myocardial peak velocity was recorded and averaged from both positions, the E/Em ratio then was calculated. Systolic (S) and diastolic (D) waves and S/D ration were calculated using pulsed wave Doppler from pulmonary venous (PV) inflow. All parameters were then compared between the groups of ≥ 50 and < 50 years of age. The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from all participants.

Statistical analysis

Continuous data are presented as the median (25th–75th percentile), while categorical data are expressed in proportions. We performed the Shapiro-Wilk test to check whether our data were normally distributed.

The majority of the analysed parameters did not have a normal distribution, even after logarithmic data transformation, thus we selected appropriate statistical analysis methods based on non-parametric tests. The presentation of the continuous data was also caused by the lack of a normal distribution for most of the analysed parameters. Comparisons between groups were performed with the Mann–Whitney U test for independent continuous data and the Pearson's chi-square test was applied for categorical data. P-values <0.05 were considered significant. The statistical analysis was conducted with the STATISTICA 9.0 (StatSoft, Tulsa OK, USA) package and R 2.25.2 environment.

Results

The HH patients' genetic characteristics were as follows: 18 persons - C282Y/C282Y genotype, 1 persons - C282Y/H63D genotype, 1 person - C282Y/wt genotype. Table 1 shows the iron turnover biochemical results, as well as haemoglobin and glycaemia level at the start of the study.

The echocardiographic parameters of all patients were in the normal range [7-8]. Comparing HH patients with healthy volunteers ≥50 years of age, significant differences were found in diastolic function parameters: IVS thickness, LVM index, Em, E/Em, PV S/D, LAA index and LAV index (Table 2).

Table 1. HH patients' laboratory characteristics at the time of first contact

	HH patients ≥50 yo n = 10*	HH patients <50 yo n = 10*	p
Iron (mcg/dl)	205 (180 – 225)	204 (181 – 225)	0.455
Ferritine (ng/ml)	472 (420 – 1052)	387 (177 – 648)	0.080
TSAT [%]	95 (80 – 100)	84 (58 – 88)	< 0.043
Haemoglobin (mg/dl)	149 (140 – 162)	149 (131 – 150)	0.201
Glycaemia (mg%)	98 (92 – 103)	92 (87 – 96)	0.120

*Data are presented as the median (25th – 75th percentile); TSAT – transferrin saturation

Table 2. Comparison of echocardiographic parameters between HH patients and healthy volunteers ≥50 yo

	Healthy volunteers; ≥50 yo n = 10*	HH patients; ≥50 yo n = 10*	p
Age	58 (54 – 62)	55 (53 – 64)	0.682
LADs (mm)	39 (35 – 40)	38 (36 – 41)	0.142
LAA index (cm ² /BSA)	8.3 (7.2 – 9.3)	11.6 (10.1 – 12.4)	<0.010
LAV index (ml/BSA)	21.8 (21.2 – 27.6)	34.9 (29.8 – 46.9)	<0.025
IVS (mm)	9.0 (7.0 – 10.0)	10.0 (10.0 – 12.0)	<0.030
PW (mm)	8.0 (7.0 – 9.5)	9.0 (9.0 – 10.0)	0.074
RWT	0.38 (0.32 – 0.43)	0.43 (0.40 – 0.47)	0.051
LVM index (g/BSA)	65.0 (56.4 – 73.0)	74.0 (67.4 – 80.8)	<0.030
E/A ratio	0.92 (0.73 – 1.06)	0.99 (0.76 – 1.29)	0.263
DT (ms)	195 (170 – 212)	191 (182 – 230)	0.263
A dur (ms)	133 (122 – 145)	147 (144 – 149)	0.059
PV S/D	1.35 (1.00 – 2.00)	1.05 (0.82 – 1.27)	< 0.048
PV Ar (cm/s)	0.30 (0.24 – 0.32)	0.31 (0.25 – 0.31)	0.402
PV Ar duration (ms)	100 (97 – 101)	98 (90 – 107)	0.231
Em	0.10 (0.09 – 0.12)	0.09 (0.07 – 0.10)	<0.046
E/Em	6.7 (6.3 – 7.5)	9.0 (8.2 – 9.0)	<0.019
LVEDD (mm)	45.0 (42.0 – 47.0)	42.5 (41.9 – 47.5)	0.422
LVESD (mm)	25.5 (23.5 – 27.5)	27.5 (25.0 – 28.5)	0.262
LVEF (%)	63 (60 – 63)	59 (58 – 60)	0.070

*Data are presented as the median (25th – 75th percentile)

LADs – left atrial diameter; BSA – body surface area; LAA index – left atrium area/BSA; LAV index – left atrium volume/BSA; IVS – intraventricular septum (mm); PW – posterior wall; RWT – relative wall thickness; LVM index – left ventricle mass/BSA; E – early mitral velocity; A – late mitral velocity; E/A – E to A ratio; DT – deceleration time of E velocity; A dur – mitral A wave duration time; PV Ar – pulmonary vein A- wave velocity; PV Ar duration – pulmonary vein A-wave duration; Em – peak mitral annulus velocity; E/Em – early mitral inflow velocity to peak mitral annulus velocity ratio; LVEDD – left ventricle end diastolic diameter; LVESD – left ventricle end systolic diameter; LVEF – left ventricular ejection fraction

Table 3. Comparison of echocardiographic parameters between HH patients and healthy volunteers <50 yo

	Healthy volunteers; <50 yo n = 10*	HH patients; <50 yo n = 10*	p
Age	39 (33 – 34)	34 (29 – 38)	0.911
LADs	35 (34 – 39)	36 (34 – 40)	0.100
LAA index (cm ² /BSA)	8.5 (8.1 – 9.0)	9.1 (8.8 – 10.2)	0.198
LAV index (ml/BSA)	22.0 (20.0 – 28.0)	25.5 (24.6 – 28.6)	0.207
IVS (mm)	9.0 (8.0 – 11.0)	8.0 (7.0 – 8.9)	0.128
PW (mm)	9.0 (7.0 – 10.0)	8.5 (7.0 – 9.3)	0.261
RWT	0.39 (0.32 – 0.43)	0.38 (0.31 – 0.43)	0.248
LVM index (g/BSA)	68.0 (66.9 – 76.0)	56.5 (49.4 – 78.0)	0.105
E/A ratio	1.54 (1.28 – 1.78)	1.53 (1.14 – 1.65)	0.312
DT (ms)	178 (148 – 191)	189 (168 – 234)	0.132
A dur (ms)	133 (108 – 150)	128 (116 – 139)	0.341
PV S/D	1.35 (1.00 – 2.01)	1.16 (0.85 – 1.41)	0.424
PV Ar (cm/s)	0.26 (0.24 – 0.30)	0.25 (0.22 – 0.28)	0.232
PV Ar duration (ms)	103 (97 – 110)	102 (92 – 131)	0.163
Em	0.14 (0.12 – 0.14)	0.14 (0.11 – 0.17)	0.311
E/Em	6.5 (5.5 – 7.8)	6.4 (5.3 – 7.9)	0.421
LVEDD (mm)	46.0 (45.0 – 47.0)	45.5 (42.8 – 48.0)	0.392
LVESD (mm)	27.0 (26.0 – 28.0)	28.0 (25.5 – 28.5)	0.280
LVEF (%)	63 (62 – 65)	58 (55 – 61)	<0.001

*Data are presented as the median (25th – 75th percentile)

LADs – left atrial diameters; BSA – body surface area; LAA index – left atrium area/BSA; LAV index – left atrium volume/BSA; IVS – intraventricular septum (mm); PW – posterior wall; RWT – relative wall thickness; LVM index – left ventricle mass/BSA; E – early mitral velocity; A – late mitral velocity; E/A – E to A ratio; DT – deceleration time of E velocity; A dur – mitral A wave duration time; PV Ar – pulmonary vein A- wave velocity; PV Ar duration – pulmonary vein A-wave duration; Em – peak mitral annulus velocity; E/Em – early mitral inflow velocity to peak mitral annulus velocity ratio; LVEDD – left ventricle end diastolic diameter; LVESD – left ventricle end systolic diameter; LVEF – left ventricular ejection fraction

In the younger subgroups we did not find the above-mentioned differences, however LVEF appeared to be lower in the younger HH subgroup than in the healthy volunteers <50 years of age (Table 3).

Discussion

Despite the lack of clinical signs of any heart disease, as well as the lack of any abnormalities in the standard echocardiographic examination, we found a number of differences between patients with newly diagnosed HH compared with healthy subjects. Previous studies focused mainly on patients with long-lasting and long-treated HH [2-4]. In our study we enrolled the patients with newly diagnosed HH, but unlike other authors we analysed echocardiographic parameters with special consideration of patient's age [5]. We found that differences regarding LV diastolic function parameters were more apparent in HH patients ≥50 years of age, whereas differences in LV systolic function were more prominent in HH patients <50 years of age when compared with healthy subjects.

Age is an independent factor affecting cardiac structure and function [1, 9-16]. Referring to the Framing-

ham and Baltimore studies, Dai et al. noted that LV wall thickness increased with age, resulting in more frequent presence of myocardial hypertrophy in older people, regardless of the prevalence of hypertension. In addition, advancing age increases the left ventricular filling pressure and, as a result, its diastolic dysfunction [9]. Moreover, enlargement of the left atrium is considered as a symptom of increased left ventricular filling pressure and is a sensitive indicator of the severity and duration of diastolic dysfunction [16].

In our study, we set an age limit of 50 years. There are publications where different cut-offs have been set, often closer to 60 years of age. For example, in a study dedicated to the echocardiographic assessment of left ventricular diastolic function, Nagueh et al. adopted age groups of 40-60 and >60 years of age [8]. Similarly, Dai et al. analysed the aging process in the heart [9]. However, in a study dedicated to diastolic dysfunction of the heart Kane et al. set the age groups at 45-64 and >65 years of age [14]. The division of age groups by every 10 years can be found in the literature, especially in large population studies [10-11, 15]. On the other hand, in a publication of the European Study Group on Diastolic Heart Failure, it was assumed that 50 years was the age limit for major changes in left ventricular

diastolic function [17]. Loffredo et al. reported that 1% of people >50 years of age have heart failure of varying aetiology [18], which confirms the legitimacy of this age limit. An additional argument for us to select the age limit of 50, is the fact that in the current era of genetic testing HH is diagnosed in a population of relatively young people. When conducting separate analyses of the ≥ 50 and < 50 years of age subgroups in our study, it was noted that the differences in diastolic parameters were present only in the older group of patients. Palka et al. [19] found significantly higher left atrium and left ventricle mass indexes in a similar age subgroup of HH patients, however, some patients included in their study were under long-term treatment by venesection.

Our results, suggesting worse left ventricle diastolic function in HH patients ≥ 50 years of age, may be explained by the influence of HH on that function, as well as the intensification of hypertrophy of the heart muscle, both of which are more advanced than they would be due to age alone. The results may even indirectly indicate a faster “heart aging” process in people with HH. Data from other studies support this hypothesis [20-21]. Using a mouse model of HH, Djemai et al. suggested a correlation between cardiomyopathy and cardiac iron deposition with aging in mice homozygous for the C282Y HFE gene [20]. Similarly, using another HH mouse model, Sukumaran et al. demonstrated that cardiac iron loading can accelerate the natural aging process of the heart, especially cardiac hypertrophy and fibrosis and potentially heart failure [21].

The above-mentioned differences in diastolic parameters were not described in the younger subgroups, but LVEF was significantly lower in HH patients. This could be explained by the greater influence of HH on systolic function in younger patients. However the small sample size in each of the age subgroups necessitates further verification of this hypothesis.

Study limitations

An important limitation of this study is its small sample size. However this is because we included only patients with an early clinical diagnosis of HH but without any cardiovascular symptoms. Although our sample is relatively small, it is similar to that in previous studies on patients with early diagnosed HH. Due to the small size of the HH group, it was not possible to perform a more advanced statistical analysis.

Conclusion

The HH patients in our study group lacked clinical symptoms of cardiovascular disease and had normal findings in the standard echocardiographic examination, however when compared with healthy subjects they had a number of abnormalities in 2D and Doppler parameters. Specifically, the HH patients < 50 years of age had abnormal LV systolic function, whereas LV diastolic dysfunction was more prominent in HH patients ≥ 50 years of age. Our findings require further corroboration on a larger patient sample and with the use of more advanced diagnostic techniques.

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