# Evaluation of left ventricular functions in individuals with iron deficiency anemia by three-dimensional echocardiography and strain imaging method

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## INTRODUCTION

Iron deficiency anemia is a common and important public health problem [1]. The World Health Organization (WHO) defines anemia as a drop in hemoglobin (Hb) value to less than 13 g/dl in male patients and 12 g/dl in women [2]. Although iron deficiency anemia (IDA) affects many systems, its effects on the cardiovascular system are particularly important. For these reasons, IDA and iron deficiency (ID) without anemia are important causes of morbidity and mortality in patients with heart failure [3–5]. Studies have shown that intravenous iron replacement given as treatment for ID without anemia in patients with heart failure provides an improvement in functional class and quality of life. This situation demonstrates the importance of ID in heart failure prognosis [6].

Although the importance of anemia and ID in heart failure has been demonstrated, it is not clear whether anemia is the cause or the result of heart failure [7]. There is no data on whether left ventricular (LV) dysfunction develops in anemic patients. This study aimed to evaluate the LV functions and subclinical LV dysfunction by two- and three-dimensional (2D, 3D) strain imaging in individuals with mild-to-moderate IDA without known cardiac disease.

## METHODS

### *Informed consent*

The participants were informed about the study and written consent was obtained. The local Ethics Committee approved the study protocol. All procedures in the study were in accordance with the 1964 Declaration of Helsinki.

### *Study design and population*

Between February 2018 and March 2019, 72 patients over the age of 18 with a diagnosis of mild-to-moderate IDA and 38 healthy volunteers were enrolled in the study. Exclusion criteria included a known disease history, regularly taking any medication, hemodynamically unstable secondary to severe anemia, and refusal to participate. In addition, it was expected that the patient group would meet the criteria for iron deficiency anemia (presented in the Supplementary material). The controls were free from known diseases, IDA criteria, and history of anemia. Since the population with iron deficiency anemia is predominantly <50 years old in female adults, the control group was recruited mostly from this age and sex range.

The patients were divided into two groups according to their Hb values indicating the severity of anemia: moderate (7–9 g/dl) and mild (≥9–12 g/dl) and were named Group A and Group B, respectively. The Hb value of the control group was ≥12 g/dl, and that group was named Group C.

Detailed physical examination was performed and routine laboratory data on the participants were recorded.

### *Iron deficiency anemia and exclusion criteria*

Diagnostic criteria for IDA and exclusion criteria were defined in the Supplementary materials.

**Table 1.** Ejection fraction and global longitudinal strain values of the study population

| Ejection fraction and global longitudinal strain parameters | | | | | | |
|---|---|---|---|---|---|---|
| | Group A (n = 19) | Group B (n = 53) | Group C (n = 38) | $P^a$ | Patient (n = 72)[b] | $P^c$ |
| 2D EF, % | 62 (62.5–69) | 64 (60–69) | 65 (62.5–69) | 0.49 | 64 (60–69) | 0.36 |
| 3D EF, % | 57.5 (56.2–65) | 57 (53–63.5) | 60 (56.2–65) | 0.16 | 57 (60–69) | 0.03 |
| 2D GLS, % | −20.35 (−22.6–[−18.1]) | −21.8 (−24.3–[−18.4]) | −19.4 (−22.6–[−18.1]) | 0.11 | −21.2 (−23.8–[−18.4]) | 0.24 |
| 3D GLS, % | −14.39 (−17–[−11]) | −15 (−19–[−12]) | −14 (−17–[−11]) | 0.42 | −15.29 (−19–[−12]) | 0.42 |

Data are given as median (interquartile range [IQR])

[a]Comparison of patients with moderate IDA (Group A), mild IDA (Group B), and control group (Group C). [b]Represents the patient population regardless of the severity of anemia. [c]Comparison of the patient population independent of the severity of anemia with the control group (Group C)

Abbreviations: 2D EF, ejection fraction evaluated by two-dimensional echocardiography; 3D EF, ejection fraction evaluated by three-dimensional echocardiography; 2D GLS, global longitudinal strain evaluated by two-dimensional echocardiography; 3D GLS, global longitudinal strain evaluated by three-dimensional echocardiography; IDA, iron deficiency anemia

### *Two- and three-dimensional ejection fraction measurement*

2D ejection fraction (EF) was calculated with the Modified Simpson method. 3D left ventricular ejection fraction (LVEF) value was obtained by EchoPAC version 6.3 (GE Vingmed US, Horten, Norway) after the apical four-, three-, and two-chamber images were obtained, and LV end-diastolic volume and end-systolic volume were determined [8].

### *Two- and three-dimensional speckle tracking strain echocardiography*

As the first step in 2D speckle tracking strain analysis, apical four-, three-, and two-chamber images were recorded, and the endocardial borders of the segments were traced manually. Global longitudinal strain (GLS) was calculated by averaging the peak systolic strain values with the help of EchoPAC.

Similarly, 3D images were evaluated offline. The end-diastole where the LV cavity is the largest and the end-systole where the cavity is the smallest were determined. The left ventricular apex, as well as mitral the annulus, were marked in both the systolic and end-diastolic periods, and the endocardial border of the long axis was determined, thus LV volume, EF, and strain parameters were obtained automatically with the software.

### *Statistical analysis*

IBM SPSS Statistics, version 24 (IBM Corp., Armonk, NY, US) was used for statistical analyses. All quantitative values are presented using median values and interquartile range (IQR). The normality of distribution was investigated with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare the patient and the control groups in the study. Relationships between quantitative variables in the patient groups were analyzed using Spearman correlation test. The difference was considered statistically significant when the *P*-value was <0.05. We tested the interobserver agreement on 15 randomly selected patients and controls with the interclass correlation coefficient (ICC). Global ICC, which represents the interobserver agreement of all measured LV parameters was 0.996. ICC for more precise measurements (GLS and EF) was 0.70 (interpreted as: 0.5–0.75 — fair to good, greater than 0.75 — excellent) [9].

## RESULTS AND DISCUSSION

### *Distribution of the groups and demographic characteristics*

There were 69 (95.8%) female and 3 (4.2%) male patients in the study. The median age was 38 (30–45) years and the median duration of IDA was 12 (1–24) months. While the median Hb value for Group A (19 patients) was 7.6 (7.1–8.3) g/dl, for Group B (53 patients) it was 10.6 (9.9–11.3) g/dl.

Group C included 38 patients, and the median Hb value was 13.2 (12.7–13.8) g/dl. The control group consisted of 36 (94.7%) female and 2 (5.3%) male patients. The median age was 45 (38.5–49) years.

When the demographic characteristics of the study group and the control group were compared, it was observed that the median age of the control group was higher (*P* = 0.03). There was no significant difference in demographic characteristics and vital signs. In the Supplementary materials, the demographic characteristics of the patient and control groups were summarized (Supplementary material, *Table S1*).

### *Ejection fraction and strain parameters*

Regardless of the severity of anemia, when the total number of anemic patients and the control group were compared, a difference was found in the 3D EF value (*P* = 0.03). However, there was no significant difference between 2D and 3D GLS values. The EF and GLS values of the patient-control group are summarized in Table 1.

Ejection fraction and GLS values were also compared according to the severity of anemia. There was no significant difference between the groups (Table 1).

Echocardiographic parameters, ferritin, and Hb values in the study group were evaluated by correlation analysis. Accordingly, a positive moderate correlation was found between the ferritin level and 2D EF (r = 0.30; *P* <0.01). Similarly, a positive but weaker relationship was shown between the ferritin level and 3D EF (r = 0.25; *P* <0.05).

It has been shown that there is a negative mild-to-moderate relationship between the 2D GLS value and the ferritin level (r = –0.30; $P < 0.05$). As a result, as ferritin levels decrease, 2D GLS values increase mathematically, meaning strain values deteriorate.

In our study, we aimed to evaluate the LV functions with the strain echocardiography method (both 2D and 3D), which can show subclinical LV dysfunction in patients with a diagnosis of IDA. Although there is no literature proving this hypothesis, it is not clear whether anemia is the cause or consequence of heart failure in preserved EF heart failure, but it should not be overlooked that anemia may be a cause of heart failure.

The patient and control groups were also compared in terms of 2D and 3D EF. The 2D EF value did not differ between the two groups ($P = 0.36$). The 3D EF value was within the normal reference range in both groups, yet it was lower in the anemic patient group compared to the control group (57% in the patient group, 60% in the control group, $P = 0.03$). When the patients were evaluated by grouping them according to the severity of anemia, no significant difference was found in terms of EF values, measured by 2D and 3D echocardiography. When Cho et al. compared anemic patients with the control group in terms of 2D EF, a statistically significant decrease was observed in EF although no statistical significance was found [10]. Similarly, in our study, it was shown that 3D EF was statistically lower when compared with the control group. In addition, 2D EF was not statistically significant in the anemic patient group in our study; it was observed to be low (64% vs. 65%).

In our study, no significant change was observed between 2D and 3D strain values in individuals with IDA compared to the control group ($P = 0.24$ for 2D GLS, $P = 0.42$ for 3D). Similarly, when the patients were grouped according to the severity of anemia, no significant difference was found in terms of GLS values measured by 2D and 3D echocardiography. In the literature, there is no study using both 2D and 3D strains in this population. There is only one study with a 3D strain assessment in anemic patients. In that study, Zhou et al. [11] reported that 3D GLS was impaired in patients in the deep anemia group (Hb, 6–9 g/dl). The patients in the mentioned study group were very different from our patient population. We may have obtained this result since we included mildly anemic patients and patients with a shorter duration of anemia in our study. While the average duration of anemia in our patients was 12 months, in the study in which 3D GLS was found significant, the average duration of anemia was 6.5 years [11].

In addition, the fact that 2D and 3D GLS values were not found to be significant when the patient and control groups were compared, may be due to the significantly higher age of the control group. In the study of Alcidi et al. [12], in which GLS was compared according to age, it was shown that GLS deteriorates with age. Especially, the decline was shown in the endocardially and epicardially measured GLS in the age group of 30–50 years.

In the literature, there are no studies evaluating the relationship between left ventricular EF and global longitudinal strain in individuals with iron deficiency without anemia. A study in iron-deficient rats without anemia showed LVEF reduction and impaired physical performance. It has been proven that the myocardium responds to iron replacement. Although our study primarily investigated the effect of anemia on LV function, a positive relationship was observed with ferritin with 2D EF and 3D EF and a negative relationship with GLS. If we consider the positive effects of the iron element on myocardial tissue in patients with heart failure, it can be speculated that low ferritin will cause a decrease in EF and deterioration in GLS [13].

Our study has several limitations. The size of the study group was small. Particularly, the size of Group A, which represents moderate IDA, was less than the control and mild anemia groups. Patients with very low hemoglobin levels were not included in the study and another limitation of our study is that the median age of the control group is higher than the patient group. Another limitation relates to the predominance of one sex. Since most of the patient population consisted of young women, the results we obtained may not be generalized to all age groups and male individuals.

## Supplementary materials

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

## Article information

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