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ORIGINAL PAPER

Evaluation of left atrial volume and function by real time three-dimensional echocardiography in anemic patients without overt heart disease before and after anemia correction

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Abstract

There are few data on the effects of low hemoglobine levels on the left atrium (LA) in anemic patients. Our aim was to evaluate left atrial (LA) volume and functions in anemic patients using real time three-dimensional echocardiography (RT3DE) and also to investigate changes in variables of LA after the correction of anemia. In total, 55 iron-deficiency anemia patients without traditional cardiovascular (CV) risk factors and 30 age- and gender-matched controls were studied. Assessments included history, physical examination and echocardiography. Of the 55 patients with anemia enrolled, 50 (39 females and 11 males 40.3 years) were followed and underwent echocardiography after correction of the anemia. LA maximum volume (LAVmax), LA minimal volume (LAVmin), LAVmax index (LAVI), before atrial contraction volume (LAVpreA), LA total emptying fraction, LA active emptying volume were higher in anemic patients. LA passive emptying fraction was significantly lower in anemic patients. Following correction of anemia, LA volume and function parameters were observed to be significantly reduced. Moreover, significant increase was noted in LA passive emptying fraction. Correlation analysis was performed and a significant negative correlation was noted between the percentage change in hemoglobin level and percentage change in LAVI ($r = -0.382$, $p = 0.003$). It was shown that volume and functions of LA are impaired in anemic patients. However impaired parameters were improved after correction of anemia. It may be thought that RT3DE LA parameters can be used as an important preclinical marker of disease pathogenesis before developing heart failure or atrial arrhythmia.

Keywords Left atrium · Left atrial volume and function · Three dimensional transthoracic echocardiography · Diastolic dysfunction

Introduction

Iron deficiency anemia is one of the most common global health problems frequently observed in daily clinical practice [1]. Anemia is a common co-morbid condition in patients with heart failure, and multiple observational studies showed an independent association between low hemoglobin and adverse cardiovascular (CV) outcomes [2, 3]. Reduction in oxygen carrying capacity of blood caused by iron deficiency leads to tissue hypoxia, and consequently structural and hemodynamic changes are observed in the heart [4]. Functional disorders develop primarily in response to decreased hemoglobin [5]. Long-term haemodynamic changes in chronic anemia increase the workload and volume burden of the heart, cause remodeling of myocytes and vessels and hypertrophy is observed on the left ventricle (LV) [6, 7]. Several published studies support the relationship between anemia and LV diastolic dysfunction in patients with cardiovascular disease, but the results are in conflict and the relationship between anemia and diastolic dysfunction is still unclear [8-10].

Previous studies showed several minor cardiovascular changes from hyperdynamic circulation to subclinical cardiac structural changes in anemic patients without overt

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heart disease [11]. However, conventional non-invasive imaging methods cannot provide detailed information about cardiac structural changes and cannot detect subtle and early functional changes associated with iron deficiency anemia [12, 13].

Left atrium (LA) volume and mechanical functions reflect the severity of LV diastolic dysfunction [14]. It is known that LA dimensions and functions are affected by LV systolic or diastolic dysfunction associated with different clinical tables such as cardiomyopathy, hypertension (HT), diabetes (DM), valvular disease and arrhythmia and they are important indicators of mortality and morbidity [15-17]. Since LA has an asymmetric structure, the reliability of two-dimensional echocardiography (2-DE) is controversial to determine its size and diameter [18]. Real-time three-dimensional echocardiography (RT3DE) is a potentially superior tool for the evaluation of complex shaped chambers with dynamic variable volumes and pressures such as LA and LV. On the other hand, RT3DE can be used to accurately assess cardiac function and LA volume while providing dynamic volumetric data [19]. Today, many RT3DE provides accurate measurement of LA volume and function and is a feasible and reproducible method for clinical benefit [20, 21].

There is not much data showing the effect of low hemoglobin level on LA structure and function in anemic patients. Therefore, it was aimed to evaluate the effects of low hemoglobin levels on LA volume and mechanical functions in RT3DE in patients with iron-deficiency anemia without overt heart disease. In addition, it was planned to investigate the effect of this improvement on LA volume and function after effective correction of anemia.

Methods

Study population

Fifty-five patients who were admitted to our hospital between July 2016 and August 2018, newly diagnosed for iron deficiency anemia having hemoglobin level below 10 g/dL and who have not received iron replacement therapy before were included into the study. Anemia defined as hemoglobin levels < 13 g/dL (hematocrit < 39%) in males, < 12 g/dL (hematocrit < 36%) in females [4]. Those having acute developing anemias, deficiency of vitamin B12 or folic acid, thalassemia, sickle cell anemia, arhythmia, ischemic heart disease, structural heart disease, DM, HT, renal failure, chronic lung disease, hypo-hyperthyroidism or any systemic disease were excluded from the study**.** Arhythmia was defined as any types of rhythms other than sinus rhythm in the electrocardiography or arrhythmic drug use. Ischemic heart disease was defined as an acute coronary syndrome history, percutaneous coronary intervention, coronary artery bypass surgery, and myocardial ischemia based on invasive or non-invasive diagnostic tests. Hypertension (HT) was defined as having at least 2 blood pressure measurements > 140/90 mmHg or using antihypertensive medications.

Systemic physical examination including blood pressure and heart rate measurements was performed. The height and weight of the patients were taken and body mass index (BMI; kg/m^2) and body surface area (BSA; m^2) were calculated. Preprandial glucose, creatinine, blood urea nitrogen (BUN), total cholesterol (TC) and triglyceride (TG) levels were measured. 12-lead electrocardiography (ECG) was performed. Advanced 2-DE and RT3DE were performed to all participants in accordance with the recommendations of the American Society of Echocardiography (ASE) by two experienced echocardiologists [22]. Subsequently, age and gender matched 30 healthy individuals (hemoglobin concentration > 13 g/dL in males and > 12 g/dL in females) were included in the study as a control group. Oral or intravenous iron replacement was applied to the 55 patients included in the our study. Patients with iron deficiency anemia were treated with oral ferrous (sulfate, fumarate, gluconate, glycine-sulfate) or ferric (protein succinylate, polymaltose complex) iron supplements. Also six different parenteral iron products were used: ferric carboxymaltose, iron sucrose and low-molecular weight iron dextran. We did not use red blood cell transfusion for anemia correction. Anemia could not be corrected in five patients in follow-up and they were excluded from the study. 50 patients were re-evaluated with advanced echocardiography at the third month after anemia correction. The mean time from iron replacement therapy initiation to the time it was assessed with RT3DE at the third month after the normal hemoglobine levels achieved was 7.1 ± 3.0 months. This study was approved by the local research ethics committee. Written consent was obtained from all patients.

Echocardiographic examination

All echocardiographic examinations were performed by two cardiologists who were blinded to the clinical data of study population using the cardiac ultrasound device (iE33, Philips Medical Systems, Andover, MA, USA), capable of performing RT3DE and has digital storage software for offline analysis. All patients had sinus rhythm during examination and all measurements were calculated from three consecutive cycles. An average of three measurements was recorded. The parameters and measurements of 2-DE and RT3DE were determined according to the ASE guidelines [22, 23].

2-DE analyses were performed using a 2.5 MHz S5-1 transducer. In the left lateral decubitus position, parasternal long and short axis, apical four-and two-chamber images were obtained. Left ventricular ejection fraction was calculated according to modified Simpson's method. The apical four-chamber view was acquired by PW Doppler method with the sample volume positioned at the tip of the mitral valve leaflets which allowed to calculate the maximum velocities of early diastolic peak transmitral flow velocity (E) and late diastolic peak transmitral flow velocity (A) in cm/s. Early (E′) and late (A′) diastolic mitral annular velocities were obtained at the septal mitral annulus level in the apical four-chamber view with septal annulus movement aligned with the sample volume line. The E/A ratio was calculated. E-wave deceleration time (DT) is calculated in milliseconds (ms).

RT3DE was performed with X3 matrix-array transducer (1–3 MHz) in order to obtain "full volume" real time pyramidal volumetric data sets along four consecutive cardiac cycles. Individuals were asked to hold their breath and images were combined with electrocardiographic records.

Apical two chamber and four chamber images were removed from the pyramidal data set during expiration. The LA gap was included in the pyramidal scanning volume. The RT3DE data sets were then digitally stored for analysis using the QLab-Philips version 9.1 software. Manually marked anatomical points used to calculate LA volumes were defined as follows, respectively: lateral, septal, anterior, inferior points of the mitral annulus and fifth point LA apex. The points determined to represent the pulmonary vein ostium or LA appendix was removed from the measurement. For each frame, LA internal endocardial margin was defined by automatic procedure and the pulmonary vein ostium and LA appendix were removed manually. A 3D LA volume model was created from these data. Digitally stored RT3DE datasets were analyzed using QLab-Philips version 9.1. All stored digital data were analyzed by a blind observer in order to calculate the following volumes: (1) LA maximum volume (LAVmax): at the end of systole, when the atrial volume was greatest just before the mitral valve opening (2) LA minimal volume (LAVmin): at the end of the diastole, when the atrial volume was lowest just before the mitral valve closure and (3) before atrial contraction volume (LAVpreA): the time corresponding to the P wave in ECG or the last frame before the mitral valve opens (Fig. 1). The obtained LAVmax index (LAVI) was calculated by dividing the LAVmax by the body surface area.

The volumes calculated with the formulas given below were chosen as parameters of LA function and were calculated using three different RT3DE LA volumes according to previous studies [24, 25]

- LA total emptying volume = LAVmax − LAVmin
- LA total emptying fraction = (LAVmax − LAVmin)/LAVmax. × 100
- LA passive emptying fraction = (LAVmax − LAVpreA)/LAVmax × 100.
- LA active emptying volume = LAVpreA − LAVmin
- LA active emptying fraction = (LAVpreA − LAVmin)/LAVpreA × 100

Statistical analysis

Continuous variables are expressed as means ± standard deviations, and categorical variables as numbers and proportions (%). Continuous variables were tested for a normal distribution with the Kolmogorov- Smirnov test and reported with approximately normal distribution. To compare the groups, independent Student *t* tests were used for continuous variables, and a chi-square test for categorical variables. Parameters measured after correction of anemia were compared with basal values using a paired *t* test. Correlations between variables were assessed with the Pearson

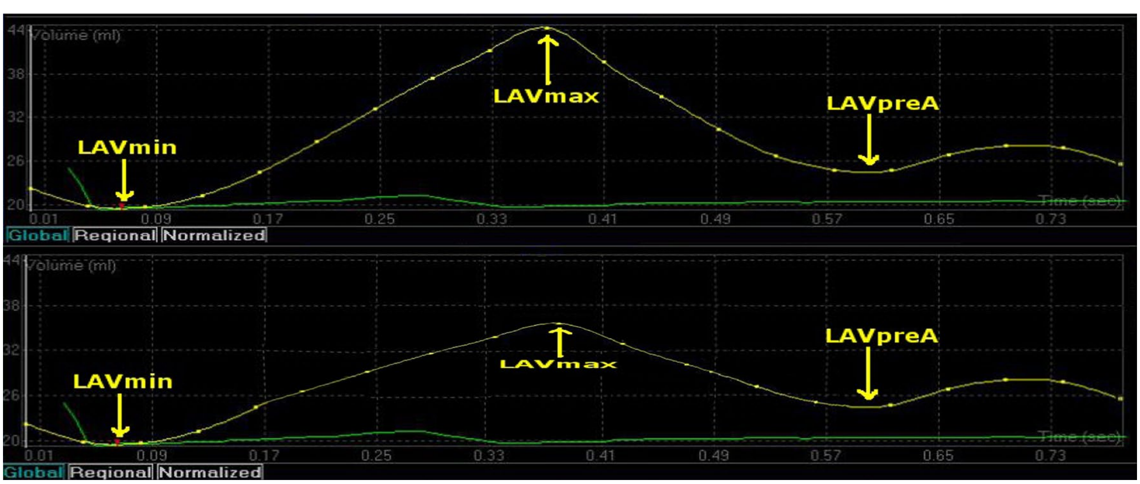

Fig. 1 time–volume curves of same patient before and after anemia correction showing left atrial maximal volume (LAVmax), left atrial minimal volume (LAVmin), and before left atrial contraction volume (LAVpreA) afer your recommendation

correlation test. A *p* value of < 0.05 was considered to indicate statistical significance. Data were processed using SPSS version 21 (SPSS, Inc., Chicago, Illinois).

Results

The main characteristics of anemic patients and the control group are summarized in Table 1. There was no significant difference between the groups in terms of age, gender, BMI, systolic or diastolic blood pressure, creatinine and serum albumin. TC, TG and hemoglobin levels were lower than the control group, although the mean heart rate was higher in the anemia group ($p < 0.001$). Ferritin, transferrin saturation, MCV and MCHC mean values were lower in patients with anemia than the previous reference values.

2-DE and Doppler measurements were compared in Table 2, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), septal wall thickness (SWT), posterior wall thickness (PWT), left atrial diameter (LAD) and ejection fraction (LVEF) were similar between control two groups. Peak E velocity, E/E′ ratio increased significantly in anemic group, although there were no significant differences in Peak A velocity, deceleration time (DT), peak E′ velocity or peak A′ velocity between two groups.

The results of LA volume and mechanical measurement with RT3DE are shown in Table 3. LAVmax, LAVmin, LAVI, LAVpreA, total emptying fraction and active emptying volume were significantly higher in anemic patients than those in controls ($p < 0.001$). Additionally, passive emptying fraction was significantly lower in anemic patients compared to controls.

In 50 of 55 patients with anemia, follow-up echocardiography was performed after correction of anemia with iron replacement therapy. Clinical features and laboratory findings of patients with anemia after iron replacement therapy are shown in Table 4. There was no significant change in BMI, systolic blood pressure, or diastolic blood pressure. At follow-up, heart rate was significantly lower and hemoglobin levels were within normal range. RT3DE variables of the anemic patients before and after treatment are shown in Table 5. LA volume parameters LAVmax, LAVmin, LAVI, LAVpreA and total emptying fraction were significantly decreased after treatment. There was also a significant increase in the passive emptying fraction. When the correlation analysis of hemoglobin and RT3DE was performed after the correction of anemia, a significant negative correlation was observed between hemoglobin percentage change and LAVI percentage change ($r = -0.382$, $p = 0.003$) (Fig. 2).

Discussion

Our study is the first to evaluate LA volume and mechanical functions using RT3DE in anemic patients without overt heart disease. LAVmax, LAVmin, LAVpreA and LA active and total emptying volume were found to be increased in anemic patients, which reflect impaired LA reservoir and booster pump functions in RT3DE. In addition, it was observed that LA passive emptying fraction was decreased

Table 1 Baseline characteristics of anemic patients and control subjects

Variable	Patients with anemia (n = 50)	Control subjects (n = 30)	*p* value
Age (year)	40 ± 11.7	39 ± 11	0.999
Gender, female (%)	39 (80)	23 (80)	0.999
BMI (kg/m^2)	27.4 ± 4.4	29.1 ± 3.6	0.121
SBP (mmHg	112.8 ± 6.1	119.9 ± 7.3	0.270
DBP (mmHg)	69.2 ± 4.4	71.0 ± 4.0	0.733
Heart rate (beats/min)	80.0 ± 10.4	71.7 ± 11.3	< 0.001
Hemoglobin (g/dL)	8.1 ± 2.9	13.0 ± 0.9	< 0.001
Creatinine (mg/dL)	0.70 ± 0.21	0.79 ± 0.16	0.071
Cholesterol (mg/dL)	125.7 ± 23.5	167.0 ± 26.6	< 0.001
Triglycerides (mg/dL)	83.9 ± 35.9	109.4 ± 46.4	< 0.001
Albumin (g/dL)	4.2 ± 0.6	4.3 ± 0.5	0.196
Ferritin (ng/dL)	7.3 ± 5.0	–	–
Transferrin saturation (%)	5.0 ± 6.9	–	–
MCV (fL)	63.7 ± 12.4	–	–
MCHC (g/dL)	28.3 ± 2.6	–	–

Values are presented as means ± standart deviations and medians with interquartile range in parentheses

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MCV* mean corpuscular volume, *MCHC* mean corpuscular hemoglobin concentration

Table 2 Two-dimensional echocardiographic variables and Doppler measurements of anemic patients and control subjects

Variable	Patients with anemia (n = 50)	Control subjects (n = 30)	*p* value
LVEDD (mm)	47.2 ± 4.9	45.2 ± 3.2	0.010
LVESD (mm)	29.0 ± 3.4	27.8 ± 2.9	0.005
SWT (mm)	8.9 ± 1.4	8.3 ± 1.2	0.084
PWT (mm)	9.7 ± 1.3	8.8.3 ± 1.2	0.046
LAD (mm)	35.5 ± 4.2	34.6 ± 3.8	0.040
EF (%)	68.6 ± 5.4	65.7 ± 4.1	0.070
Peak E velocity (m/s)	0.85 ± 0.1	0.71 ± 0.2	< 0.001
Peak A velocity (m/s)	0.67 ± 0.1	0.60 ± 0.1	0.034
DT (ms)	196.8 ± 35.6.0	195.0 ± 24.3	0.897
Peak E′ velocity (cm/s)	14.2 ± 3.9	12.7 ± 1.9	0.225
Peak A′ velocity (cm/s)	9.9 ± 2.9	8.8 ± 1.8	0.303
E/E′	7.9 ± 1.7	6.0 ± 1.3	< 0.001

Values are presented as means ± standart deviations and medians with interquartile range in parentheses

LVEDD left ventricular end-diastolic diameter, *LVESD* left ventricular end-systolic diameter, *SWT* septal wall thickness, *PWT* posterior wall thickness, *LAD* left atrial diameter, *EF* ejection fraction, *E* mitral early diastolic, *A* mitral late diastolic, *DT* deceleration time of mitral inf low velocity, *E′* mitral annular early diastolic, *A′* mitral annular late diastolic

Table 3 Real time three dimensional echocardiographic left atrial volume and function variables of anemic patients and control subjects

	Patients with anemia n:50	Control subjects n:30	p
LAVmax (mL)	42.3 ± 11.4	35.6 ± 2.5	< 0.001
LAVmin (mL)	18.1 ± 5.3	12.6 ± 2.3	< 0.001
LAVI (mL/m^2)	26.8 ± 3.0	20.5 ± 2.4	< 0.001
LAVpreA (mL)	28.6 ± 9.1	19.6 ± 1.9	< 0.001
LA total emptying volume (mL)	24.7 ± 6.3	22.6 ± 1.1	0.005
LA total emptying fraction (%)	57.9 ± 48	61.5 ± 2.7	0.001
LA active emptying volume (mL)	11.2 ± 4.0	7.8 ± 2.33	< 0.001
LA active emptying fraction (%)	37.6 ± 5.0	35.1 ± 7.41	0.025
LA passive emptying fraction (%)	32.8 ± 5.7	39.6 ± 9.13	< 0.001
Expansion index	141.1 ± 19.5	144.5 ± 22.6	0.472

Values are presented as means ± standart deviations and medians with interquartile range in parentheses

LA left atrium, *LAVmax* LA maximum volume at end-systole, *LAVmin* LA minimum volume at end-diastole, *LAVI* LA maksimum hacim indeksi, *LAVpreA* LA volume before atrial contraction

Table 4 Clinical features and laboratory findings of anemic patients (n = 50) before and after anemia correction

	Before anemia correction	After anemia correction	p
BMI (kg/m^2)	27.3 ± 4,4	27.5 ± 3.6	0.121
SBP (mmHg)	117.8 ± 6.1	120.9 ± 7.3	0.270
DBP (mmHg)	73.2 ± 4.4	72.7 ± 4.0	0.733
Heart rate (beats/min)	83.3 ± 10.4	72.7 ± 11.3	< 0.001
Hemoglobin (g/dL)	7.9 ± 2.7	12.4 ± 0.7	< 0.001

Values are presented as means ± standart deviations and medians with interquartile range in parentheses

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

with LA conduit function change. This study showed that LA volume was increased and LA mechanical function was deteriorated in anemic patients. A significant improvement was observed in LA volume and mechanical functions after the correction of anemia.

The low level of hemoglobin in anemic patients was shown to be an important factor in increasing cardiac output to provide adequate oxygen support to the tissues [26]. Georgieva and Georgieva showed that the transition from compensatory stage in which cardiac output is high in patients with anemia to decompensated stage in which LV dysfunction is evident started at the hemoglobin level below 7 g/dL [27]. Decrease in hemoglobin level was found to be closely associated with increased morbidity and mortality in

Table 5 Three dimensional echocardiographic left atrial volume and function variables of anemic patients (n:50) before and after anemia correction

	Before anemia correction	After anemia correction	p
LAVmax (mL)	42.3 ± 11.4	36.5 ± 9.4	< 0.001
LAVmin (mL)	18.1 ± 5.3	15.8 ± 6.4	0.001
LAVmax index (mL/m^2)	26.8 ± 3.0	23.9 ± 2.7	< 0.001
LAVpreA (mL)	28.6 ± 9.1	23.9 ± 7.1	< 0.001
LA total emptying volume (mL)	24.7 ± 6.3	21.4 ± 5.3	< 0.001
LA total emptying fraction %	57.9 ± 48	58.6 ± 6.0	0.426
LA active emptying volume (mL)	11.2 ± 4.0	9.3 ± 2.9	< 0.001
LA active emptying fraction %	37.6 ± 5.0	35.6 ± 6.7	0.040
LA passive emptying fraction %	32.8 ± 5.7	39.6 ± 7.3	0.001
Expansion index	141.1 ± 19.5	145.5 ± 22.1	0.249

Values are presented as means ± standart deviations and medians with interquartile range in parentheses

LA left atrium, *LAVmax* LA maximum volume at end-systole, *LAVmin* LA minimum volume at end-diastole, *LAVI* LA maksimum hacim indeksi, *LAVpreA* LA volume before atrial contraction

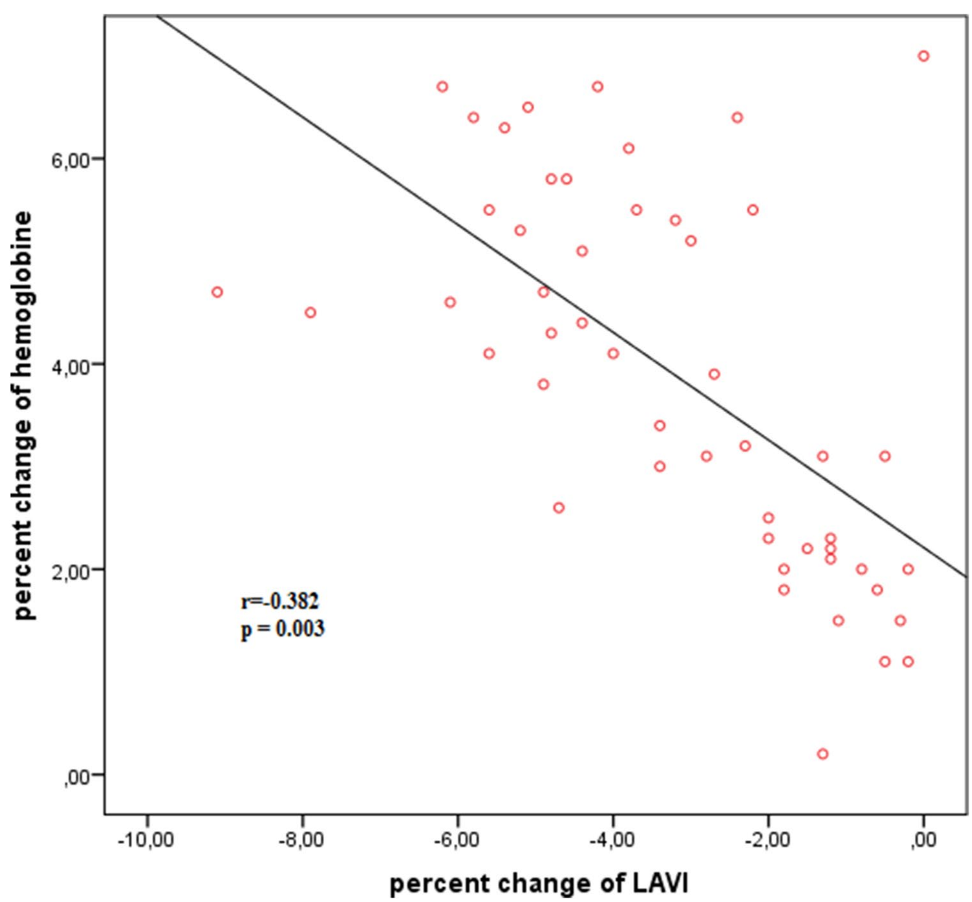

Fig. 2 Scatter plot showing the correlation between the percent change in hemoglobin level and change percent change of LAVI in the anemic patients after correction of anemia

different clinical tables [28]. Therefore, early diagnosis and treatment of iron deficiency can greatly improve quality of life and reduce hospitalization and morbidity and ultimately lead to a reduction in health expenditure [29].

To date, most studies on anemia have been based on LV systolic function and mass indexes, and the association of anemia with LV diastolic dysfunction had not been stated clearly. In the study of Cho et al. there was a relationship between the low hemoglobin and LV structures and filling pressures. They showed that LVEDD, LVESD, LAVI and E / E’ ratios significantly changed after the improvement of low hemoglobin levels in anemic patients [13]. Shen et al.

evaluated LA function in anemic patients with 2D-STE, and conventional echocardiography parameters, strain and strain rate of LA and longitudinal strain of LV changed with the decrease in hemoglobin concentration [30]. We demonstrated the change (deterioration) of LA functions with RT3DE which is more sensitive that supports the findings of this study.

LA functions are important factors affecting cardiac output by regulating the filling pressure of the LV with reservoir, conduit and pump tasks [31]. Therefore, we can say that the structural and functional remodeling of LA is clinically important [32]. Nowadays, RT3DE may show atrial dysfunction prior to clinical findings and at earlier stages compared to the evaluation with standard echocardiography. Indeed, 2-DE parameters and most of the pulse Doppler measurements were in the normal range in our study. In contrast, most of the LA volume and volume parameters determined by RT3DE were abnormal. Previous studies in different patient groups showed that RT3DE is a reliable method for the measurement of LA volume and function, and a suitable and reproducible method for clinical application [20, 21, 25].

Diastolic dysfunction was proven in individuals with anemia with the increase in LAVmax, LAVmin and LAVpreA which shows the reservoir function receiving the blood from pulmonary veins during LV systole. Blood flow from LA to LV was impaired by decreased LV compliance, and as shown in our study, increase in LA volume and LA contractile functions, whereas LA remission in LA conduit function was observed correspondingly [33, 34]. This increase in LAVmax and LAVpreA was attributed to the increase in LV filling pressure. The results obtained in our study also confirm diastolic dysfunction, LAVmax and LAVmin reservoir function were higher in anemic patients than in the control group and the volume was decreased with the correction of anemia.

Our results also indicate that the increase in LAVI is related to the compensatory mechanism in LA contraction. A decrease in LA passive emptying fraction indicates an impairment of atrial conduit function [35]. The deterioration in the LA passive emptying fraction also contributes to the larger residual LA volume before the active contraction. The increase in LAVI and fiber length occurs with increased LA contraction forces (Frank-Starling mechanism) [36, 37]. In addition, the hyperdynamic status of patients with anemia in our study was consistent with previous studies [10, 11]. Increase in LA volume and conduit function together with decreased LA conduit function are expected to be associated with impaired LV compliance [22]. When evaluated with LAVI, hemoglobin reduction is strongly associated with LV filling pressure. These functional and hemodynamic changes in LA associated with anemia regressed with proper correction of the low hemoglobin level. In our study, a correlation was found between the percentage of change in hemoglobin level and LAVI in anemic patients after the improvement of anemia. Therefore, our results show that the increase in LV filling pressure and LA volume may be significant steps in the progression from anemia to heart failure and LV and LA volume and pressure changes can be recovered by effective improvement of hemoglobin levels.

Limitations

We acknowledge that our study has some limitations. First, our study had a relatively small sample size and we did not have long-term follow-up data. Second, LA strain measurement was not performed to facilitate an understanding of LA physiology in anemic patients. In addition, LA appendix plays an important role in LA reservoir function, especially during LA pressure or volume increase. However, we did not include the LA appendix for the calculation of LA volume and function. Our study population composed of anemia patients who were newly diagnosed and who have not received iron replacement therapy before. It may be difficult for these patients to know the initiation time of the disease and to determine the duration of the disease.

Conclusion

It was shown with RT3DE that volume and function of LA were impaired in anemic patients. However, improvement was observed in findings after effective correction of anemia. It can be thought that LA volume parameters can be used as an important preclinical marker of disease pathogenesis in RT3DE before developing heart failure or atrial arrhythmia in the management of anemic patients.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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