ORIGINAL ARTICLE

# Iron deficiency and hematinic deficiencies in atrial fibrillation: A new insight into comorbidities

## Atriyal fibrilasyonda demir eksikliği ve hematinik eksiklikler: Eşlik eden hastalıklara yeni bir bakış açısı

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## ABSTRACT

***Objective:*** Iron deficiency (ID) is the most common nutritional deficiency, and iron metabolism becomes further deteriorated in the presence of certain conditions, such as heart failure (HF). Atrial fibrillation (AF) has many similarities to HF, including a chronic inflammatory pathophysiology; however, the prevalence of ID and other hematinic deficiencies in AF patients have not been determined.

***Methods:*** In this study, the prevalence of iron (serum ferritin <100 μg/L or ferritin 100–299 μg/L with transferrin saturation <20%), vitamin B12 (<200 pg/mL), and folate deficiency (<4.0 ng/mL) was evaluated in 101 patients with non-valvular AF with preserved left ventricular ejection fraction and no signs of HF, and the results were compared with 35 age- and gender-matched controls.

***Results:*** Anemia was detected in 26% of the patients. A total of 48 (47.6%) patients had ID, 10 (9.9%) had a vitamin B12 deficiency, and 13 (12.9%) had a folate deficiency. The prevalence of ID was similar in the controls and the paroxysmal AF patients, but increased gradually in persistent and permanent AF. Univariate logistic regression analysis demonstrated that permanent vs. paroxysmal AF [Odds ratio (OR): 2.17; 95% confidence interval (CI): 0.82–5.69; p=0.011], high sensitive C-reactive protein (OR: 1.47; 95% CI: 0.93–2.36; p=0.019), N-terminal pro b-type natriuretic peptide (OR: 1.24; 95% CI: 0.96–1.71; p=0.034), and white blood cell count (OR: 1.21; 95% CI: 0.95–1.58; p=0.041) were associated with ID. In multivariable analysis, permanent AF remained as an independent clinical associate of ID (OR: 4.30; 95% CI: 0.83–12.07; p=0.039).

***Conclusion:*** ID is common in permanent AF, as in HF. Inflammation and neurohormonal activation seem to contribute to its development.

## ÖZET

***Amaç:*** Demir eksikliği (DE) en sık görülen nutrisyonel eksikliktir ve kalp yetersizliği (KY) gibi bazı durumların varlığında demir metabolizmasında daha ciddi bozukluklar meydana gelebilir. KY ve atriyal fibrilasyonun (AF) kronik enflamatuvar patofizyoloji ve diğer birçok sayıdaki ortak özelliklerine rağmen AF hastalarında DE ve diğer hematinik eksikliklerin prevelansı ortaya konulmamıştır.

***Yöntemler:*** Bu çalışmada, demir (serum ferritin <100 μg/L veya ferritin 100–299 μg/L olmakla beraber transferrin satürasyonu <20%), vitamin B12 (<200 pg/mL) ve folat eksikliği (<4.0 ng/mL) valvüler olmayan AF tanısı olup korunmuş sol ventrikül ejeksiyon fraksiyonuna sahip KY semptomu olmayan 101 hastada değerlendirildi ve sonuçlar yaş ve cinsiyet bakımından benzer 35 kontrol hastasıyla karşılaştırıldı.

***Bulgular:*** Hastaların %26'sında anemi saptandı. Toplam 48 (%47.6) hastada DE, 10 (%9.9) hastada vitamin B12 eksikliği ve 13 (%12.9) hastada folat eksikliği saptandı. Kontrol ve paroksismal AF grupları arasındaki DE prevelansı benzer olmakla beraber persistan ve permanent AF hastalarında DE prevelansı tedrici artış göstermekteydi. Tek değişkenli lojistik regresyon analizinde paroksismale kıyasla permanent AF [Odds oranı (OO): 2.17; 95% güven aralığı (GA): 0.82–5.69; p=0.011], yüksek duyarlı C-reaktif protein (OO: 1.47; 95% GA: 0.93–2.36; p=0.019), N-terminal pro b-tip natriüretik peptid (OO: 1.24; 95% GA: 0.96– 1.71; =0.034) ve beyaz kan hücresi sayısı (OO: 1.21; 95% GA: 0.95–1.58; p=0.041) DE ile ilişkili saptandı. Çoklu değişkenli analizde ise permanent AF, DE ile bağımsız olarak ilişkili tek klinik değişken olarak saptandı (OO: 4.30; 95% GA: 0.83–12.07; p=0.039).

***Sonuç:*** DE permanent AF'de aynen KY'de olduğu gibi sık olarak görülür. Enflamasyon ve nörohormonal aktivasyonun bu duruma katkısı göze çarpmaktadır.

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Iron has unique biochemical features and plays an important role in hematopoiesis, the synthesis and degradation of macromolecules, oxygen storage and transport, and oxidative metabolism in the heart and skeletal muscle.[1–3] Iron deficiency (ID) is the most common nutritional deficiency worldwide, affecting more than one-third of the population.[4] ID with and without anemia causes reduced aerobic performance, poor physical condition, decreased cognitive function, dizziness, shortness of breath, restless legs syndrome, and hair loss, whereas iron supplementation improves symptomatic, cognitive, and exercise performance.[5–7]

Chronic inflammatory diseases, especially autoimmune diseases, like inflammatory bowel disease, are characterized by abnormal iron metabolism.[8] Ferritin, which is both a marker for ID and an acute phase reactant, increases in these conditions, and a relatively higher level of ferritin (30–100 ng/mL) is accepted as sufficient to diagnose ID, in contrast to with individuals without chronic inflammatory conditions (ferritin <30 ng/mL). Besides ferritin, transferrin saturation (Tsat) may also be used to diagnose ID with a similar cut-off level for the general population (i.e., <20%). Tsat is a marker for iron utilization. Normally, 16% to 45% of transferrin is saturated with iron, and a reduced Tsat has a high sensitivity (90%) for detecting ID status, despite having a poor specificity (40–50%).

The prevalence and possible consequences of ID in cardiovascular disorders, particularly in heart failure (HF), has been investigated extensively.[9–11] Correction of ID in HF results in a significant improvement in functional capacity, symptoms, and quality of life, and significantly reduces hospitalizations due to worsening HF.[10,12]

AF is the most common chronic arrhythmia, affecting 1% to 2% of the general population, and its prevalence increases with aging. It is estimated that 1 in 4 middle-aged adults in Europe and in US will develop AF.[13] HF and AF coincide in many patients and share common pathophysiologies with similar risk factors. AF is one of the major causes of HF, sudden death, and stroke.[14] AF and HF can trigger and exacerbate each other through several mechanisms, such as structural remodeling, activation of neurohormonal pathways, and tachycardia-related impairment of left ventricular function. AF is also characterized by a chronic inflammatory status, which increases the risk for thromboembolic events, creating a vicious circle between these 2 conditions.[15]

**Abbreviations:**

| | |
|---|---|
| *AF* | *Atrial fibrillation* |
| *BMI* | *Body mass index* |
| *eGFR* | *Estimated glomerular filtration rate* |
| *HF* | *Heart failure* |
| *Hs-CRP* | *High-sensitivity C-reactive protein* |
| *ID* | *Iron deficiency* |
| *NLR* | *Neutrophil-to-lymphocyte ratio* |
| *NT-proBNP* | *N-terminal pro-type B natriuretic peptide* |
| *NVAF* | *Non-valvular AF* |
| *TIBC* | *Total iron-binding capacity* |
| *Tsat* | *Transferrin saturation* |
| *WBC* | *White blood cell* |

Anemia is a frequently encountered problem in AF, with a prevalence of approximately 12%.[16,17] Anemia in AF is related to older age, an increase in mortality, hospitalization, risk of bleeding, and possibly thromboembolic events.[18] Due to its association with increased bleeding risk after the initiation of oral anticoagulant therapy, 2 bleeding risk scores [the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score and the Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke (HEMORR2HAGES) score] included the presence of anemia as a component of risk assessment. Despite the clear interaction between anemia and unfavorable events in AF, existing studies have not determined the precise type. As ID is the most important cause of anemia, it is reasonable to anticipate that it is the most frequent type of anemia in AF patients on chronic anticoagulant therapy. To test this hypothesis, the aim of this study was to evaluate ID and other hematinic parameters in patients with AF and compare the results with an age- and gender-matched control group.

## METHODS

Consecutive patients with confirmed non-valvular AF (NVAF) presenting at the outpatient anticoagulation clinic of the Sultan Abdulhamid Han Training and Research Hospital between May and July 2017 were evaluated retrospectively. All of the patients were taking warfarin for oral anticoagulation and had come for routine prothrombin time follow-up. The inclusion criteria for the study were a documented history of NVAF of >6 months, left ventricular ejection fraction >50% as assessed with the Simpson's planimetric method on echocardiography, and unchanged medication for ≥1 month prior to the study. The exclusion criteria included any significant valvular disease, any

major surgery in the previous 3 months, recent acute coronary syndrome, any acute or chronic illness that might affect iron metabolism (including infection, inflammatory diseases, severe renal failure requiring hemodialysis, known hematological disease or malignancy), lack of the hematinic tests investigated in this study, and any treatment for anemia and/or ID in the 12 months prior. Ferritin level, Tsat, and the prevalence of ID and anemia were compared with an age- and gender-matched control group (n=35) who had no AF or HF and none of the study exclusion criteria. No upper age limit was used.

Clinical information, and laboratory and demographic data were obtained from hospital records. NVAF was defined as the detection of an AF episode lasting longer than 30 seconds without a reversible or transient etiology and the absence of mitral stenosis or prosthetic heart valve, whereas annuloplasty with or without a prosthetic ring, commissurotomy, and/or valvuloplasty were permitted. The pattern of AF was presented as paroxysmal, persistent, or permanent. Paroxysmal AF was defined as self-terminating AF or AF terminated by direct current cardioversion up to 7 days. Persistent AF was defined as AF that lasts longer than 7 days, including episodes that are terminated by either pharmacological or direct current cardioversion after 7 days or more. Permanent AF was defined as AF that has lasted more than 1 year and is accepted by the patient and physician.

Complete blood count testing was performed with a Coulter LH 780 hematology analyzer (Beckman Coulter Inc., Brea, CA, USA) for hemoglobin, hematocrit, white blood cell (WBC) count, and platelet count measurement. Inflammatory status was evaluated according to WBC, neutrophil-to-lymphocyte ratio (NLR) and high-sensitivity CRP (hs-CRP) levels. The Hs-CRP level was measured with a Cobas Integra analyzer (Roche Diagnostics, Basel, Switzerland) using a turbidimetric method. Anemia was defined as a hemoglobin level <12 g/dL in women and <13 g/dL in men. Serum concentrations of serum iron, ferritin, and total iron-binding capacity (TIBC) were assessed directly. Tsat was calculated as a ratio of serum iron to TIBC, multiplied by 100, and expressed as a percentage. The serum ferritin level was determined by electrochemiluminescence immunoassay (ARCHITECT i2000SR immuno-assay analyzer; Abbott Diagnostics, Lake Forest, IL, USA). Serum iron and TIBC were assessed using a substrate method with ferene-S and an ARCHITECT c16000 clinical chemistry analyzer (Abbott Diagnostics, Lake Forest, IL, USA). Vitamin B12 and folic acid were measured with an automated analyzer (ARCHITECT; Abbott Diagnostics, Lake Forest, IL,USA).

ID in AF patients was defined according to the HF guidelines as a serum ferritin level of <100 $\mu$g/L or a serum ferritin level of 100–299 $\mu$g/L with a Tsat of <20%. In the controls, ID was defined as a serum ferritin level of <30 $\mu$g/L and/or Tsat of <20%. The definitions for vitamin B12 (<200 pg/mL) and folate (<4.0 ng/mL) deficiency were the same for both groups. Renal function was assessed using the estimated glomerular filtration rate (eGFR, mL/minute/1.73 $m^2$), calculated with the Chronic Kidney Disease Epidemiology Collaboration equation. N-terminal pro-type B natriuretic peptide (NT-proBNP) was measured using electrochemiluminescence immunoassay with the ARCHITECT i2000SR immuno-assay analyzer.

## Statistical analysis

The Kolmogorov-Smirnov test was used to test normality. Continuous variables with normal distribution were expressed as mean±SD. Continuous variables with skewed distribution were expressed as median and interquartile range. Continuous variables with normal distribution were compared using an independent sample T-test; continuous variables with skewed distribution were compared with the Mann-Whitney U test. Categorical variables were expressed as number and percentage and the Pearson's chi-square or the Fisher's exact test was used to evaluate the difference. Clinical determinants of ID in patients with NVAF were established using univariate and multivariable logistic regression models. The following variables were included in these analyses: age; gender; body mass index (BMI); pattern of AF; presence of hypertension or diabetes mellitus; smoking; therapy with beta-blocker, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, propafenone, amiodarone, or diuretic; and laboratory variables of glucose, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, eGFR, hs-CRP, NT-proBNP, WBC, and NLR. A 2-tailed p value of <0.05 was considered statistically significant. Analyses were performed using SPSS for Windows, Version 16.0. (SPSS Inc., Chicago, IL, USA).

## RESULTS

The initial study group consisted of 127 consecutive patients with NVAF. A total of 26 patients were excluded as a result of meeting at least 1 of the exclusion criteria. Among the remaining 101 NVAF patients (mean age: 67.0±9 years; males: 42.5%), anemia was detected in 26 (25.7%) patients, compared with 5 subjects (14%) in the control group (p=0.164). Irrespective of the presence of anemia, ID was detected in 48 (47.6%) patients. Among them, 20 (19.8%) had a ferritin level <30 μg/L and all had a ferritin level <100 μg/L. A Tsat of <20% was detected in 45 (93.8%) of the ID patients. The frequency of ID in the control group was significantly less than in the AF patients (20%; p=0.005). The prevalence of B12 deficiency in NVAF patients was 9.9%, and folic acid deficiency was detected in 12.9% of the patients.

The baseline characteristics of the patients with and without ID are summarized in Table 1. Age, distribution of male gender, and BMI were similar between the 2 groups. Patients with ID had a similar prevalence of anemia (33.3% vs. 18.9%; p=0.097) compared with the non-ID group. The history of hypertension, diabetes mellitus, hyperlipidemia, cardiovascular event, chronic lung disease, and drug and alcohol use were also similar between groups. The mean CHA2DS2-VASc score (congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism, vascular disease, age 65-74 years, female sex) was not different between AF patients with or without ID (2.54±1.38 vs. 2.54±1.37; p=0.984). The results of laboratory analysis revealed that patients with Id had a higher hs-CRP and NT-pro-BNP level and WBC count.

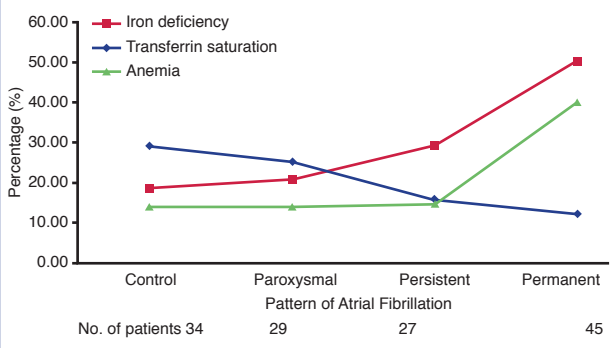


**Figure 1.** Rates of iron deficiency, anemia and transferin saturation. Each x-axis interval is equal to or greater than the lower limit of the interval and less than the upper limit. Numbers of rates and saturations are listed in Table 1.

The prevalence of anemia in the control group and those with paroxysmal, persistent, and permanent AF was 14.0%, 13.8%, 14.8%, and 40.0%, respectively (p<0.001) (Fig. 1). Univariate logistic regression models demonstrated that permanent vs. paroxysmal AF [odds ratio (OR): 2.17; 95% confidence interval (CI): 0.82–5.69; p=0.011], hs-CRP (OR: 1.47; 95% CI: 0.93–2.36; p=0.019), NT-pro-BNP (OR: 1.24; 95% CI: 0.96–1.71; p=0.034), and WBC count (OR: 1.21; 95% CI: 0.95–1.58; p=0.041) were associated with ID (Table 2). Based on a multivariable logistic regression model, only permanent vs. paroxysmal AF remained as an independent clinical associate with ID (OR: 4.30; 95% CI: 0.83–12.07; p=0.039).

## DISCUSSION

The results of this study indicated that ID with or without anemia was common in patients with NVAF, especially in those with permanent AF, affecting nearly half of all study patients. Inflammatory and neurohumoral markers were associated with ID in AF patients as in HF patients; however, they were not independent determinants of ID in this study group. Other hematinic deficiencies were infrequent in NVAF patients.

The prevalence of anemia in our study group was considerably higher (26%) than the previously reported rates for patients with AF (12%) and controls (14%). Despite the exclusion of patients with systolic dysfunction and overt signs of HF, the prevalence of ID in the study group (47%) was similar to previously reported ratios in HF studies. These findings may be explained by several factors, including the relatively older age of the patients, subclinical blood loss due to chronic warfarin usage, and subclinical systemic congestion in the liver or gastrointestinal tract. It should be kept in mind that we used different criteria for the definition of ID in the study group and the controls. When we applied the same criteria for a low ferritin level (i.e., <30 ng/mL), the frequency of ID in AF was the same as seen in the controls. Nevertheless, the frequency of AF patients with ID and a Tsat of <20% was again higher than that observed in the controls, and almost all of the AF patients with ID had a low Tsat ratio.

Absolute ID with a reduced ferritin level occurs due to the depletion of the body's iron stores and is

**Table 1. Baseline characteristics of patients with non-valvular atrial fibrillation with and without iron deficiency**

| | Patients with AF and no ID* (n=53) | Patiens with AF and ID (n=48) | *p* |
|---|---|---|---|
| Age (years) | 66±8 | 68±9 | 0.209 |
| Sex (males) | 23 (43.4) | 20 (41.7) | 0.861 |
| Body mass index (kg/m$^2$) | 28 (25–32) | 28 (25–30) | 0.446 |
| Pattern of atrial fibrillation | | | |
| Paroxysmal | 19 (35.8) | 10 (20.8) | 0.096 |
| Persistent | 13 (24.5) | 14 (29.2) | 0.599 |
| Permanent | 21 (39.6) | 24 (50.0) | 0.295 |
| Hypertension | 36 (67.9) | 35 (72.9) | 0.583 |
| Diabetes mellitus | 15 (28.3) | 8 (16.7) | 0.164 |
| Hyperlipidemia | 7 (13.2) | 8 (16.7) | 0.625 |
| Current smoking status | 2 (3.8) | 4 (8.3) | 1.000 |
| Drink alcohol | 2 (3.8) | 0 (0.0) | 1.000 |
| Cerebrovascular event | 2 (3.8) | 2 (4.2) | 1.000 |
| Coronary artery disease | 17 (32.1) | 15 (31.2) | 0.929 |
| Chronic lung disease | 5 (9.4) | 6 (12.5) | 0.621 |
| Anemia | 10 (18.9) | 16 (33.3) | 0.097 |
| Treatment | | | |
| Aspirin | 1 (1.9) | 1 (2.1) | 1.000 |
| Clopidogrel | 3 (5.7) | 3 (6.2) | 0.900 |
| Beta-blocker | 41 (77.4) | 36 (75.0) | 0.781 |
| Propafenone | 4 (7.5) | 2 (4.2) | 0.473 |
| Amiodarone | 3 (5.7) | 3 (6.2) | 0.900 |
| Digoxin | 2 (3.8) | 5 (10.4) | 0.252 |
| Angiotensin-converting enzyme inhibitor | 19 (35.8) | 18 (37.5) | 0.863 |
| Angiotensin receptor blocker | 15 (28.3) | 9 (18.8) | 0.260 |
| Calcium channel blocker | 9 (17.0) | 7 (14.6) | 0.742 |
| Diuretic | 9 (17.0) | 11 (22.9) | 0.455 |
| Laboratory analysis | | | |
| Glucose (mg/dL) | 103 (95–119) | 105 (94–137) | 0.935 |
| Alanine aminotransferase (IU/L) | 20 (16–25) | 16 (13–27) | 0.102 |
| Aspartate aminotransferase (IU/L) | 22 (17–27) | 20 (16–29) | 0.479 |
| Blood urea nitrogen (mg/dL) | 18 (14–25) | 17 (14–21) | 0.364 |
| Creatinine (mg/dL) | 1.01±0.34 | 0.97±0.29 | 0.500 |
| eGFR (mL/min/1.73 m$^2$) | 66 (51–84) | 68 (57–77) | 0.644 |
| High sensitivity C-reactive protein (mg/L) | 0.4 (0.2–0.8) | 0.7 (0.3–1.0) | 0.002 |
| N-terminal pro-B type natriuretic peptide (pg/mL) | 120 (64–191) | 191 (104–312) | 0.003 |
| Iron (μg/dL) | 77 (60–95) | 49 (39–68) | <0.001 |
| Ferritin (μg/L) | 112 (51–146) | 42 (25–58) | <0.001 |
| Total iron binding capacity (μg/dL) | 239 (206–281) | 277 (227–312) | 0.002 |
| Transferrin saturation (%) | 24 (15–28) | 13 (11–16) | <0.001 |
| Cobalamin (pg/mL) | 289 (232–355) | 309 (241–483) | 0.297 |
| Vitamin B12 deficiency | 6 (11.3) | 4 (8.3) | 0.616 |
| Folic acid (ng/mL) | 6.8 ± 3.1 | 6.6±2.6 | 0.176 |
| Folic acid deficiency | 6 (11.3) | 7 (14.6) | 0.625 |
| White blood cell count (cells/μL) | 7.3±2.1 | 8.0±2.3 | 0.034 |
| Neutrophil-to-lymphocyte ratio | 2.50±1.39 | 2.54±1.29 | 0.902 |
| Platelet count (cells/μL) | 232 (183–261) | 214 (180–293) | 0.644 |
| Hematocrit (%) | 39±4 | 38±4 | 0.973 |
| Hemoglobin (g/dL) | 13.1±1.6 | 12.7±1.5 | 0.674 |

AF: Atrial fibrillation; ID: Iron deficiency; eGFR: Estimated glomerular filtration rate. *ID was defined as ferritin <100 mg/L, or ferritin 100–300 mg/L and Tsat <20%. Data are presented as mean±SD, median (with lower and upper quartiles), or number (with percentage), as appropriate.

**Table 2. Clinical determinants of iron deficiency* in patients with atrial fibrillation (univariate and multivariable logistic regression models)**

| | Univariate models | | | Multivariable model | | |
|---|---|---|---|---|---|---|
| Determinants | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Age | 1.02 | 0.97–1.06 | 0.398 | 1.01 | 0.93–1.41 | 0.648 |
| Sex (males vs. females) | 0.93 | 0.42–2.05 | 0.861 | 0.96 | 0.29–2.16 | 0.489 |
| Body mass index | 0.97 | 0.90–1.04 | 0.441 | 0.97 | 0.92–1.33 | 0.716 |
| Persistent vs. paroxysmal atrial fibrillation | 2.04 | 0.69–5.99 | 0.192 | 3.31 | 0.62–7.52 | 0.159 |
| Permanent vs. paroxysmal atrial fibrillation | 2.17 | 0.82–5.69 | 0.011 | 4.30 | 0.83–12.07 | 0.039 |
| Hypertension | 1.27 | 0.53–3.00 | 0.584 | 1.13 | 0.69–4.86 | 0.614 |
| Diabetes mellitus | 0.90 | 0.79–2.86 | 0.168 | 0.92 | 0.81–1.87 | 0.365 |
| Smoking | 2.31 | 0.40–13.26 | 0.345 | 1.73 | 0.58–9.66 | 0.318 |
| Treatment | | | | | | |
| Beta-blocker | 0.87 | 0.35–2.19 | 0.781 | 0.92 | 0.55–3.20 | 0.901 |
| Propafenone | 0.73 | 0.39–3.04 | 0.479 | 0.83 | 0.44–4.66 | 0.515 |
| Amiodarone | 1.11 | 0.61–5.78 | 0.900 | 1.19 | 0.77–8.13 | 0.740 |
| Digoxin | 2.96 | 0.54–16.05 | 0.207 | 2.02 | 0.56–8.81 | 0.466 |
| Angiotensin-converting enzyme inhibitor | 1.07 | 0.47–2.41 | 0.863 | 1.11 | 0.78–5.61 | 0.861 |
| Angiotensin receptor blocker | 0.88 | 0.42–3.49 | 0.763 | 0.91 | 0.54–4.57 | 0.952 |
| Calcium channel blocker | 1.15 | 0.68–1.95 | 0.580 | 1.22 | 0.73–6.24 | 0.843 |
| Diuretic | 1.45 | 0.54–3.88 | 0.456 | 1.19 | 0.34–4.16 | 0.501 |
| Laboratory variables | | | | | | |
| Glucose | 1.00 | 0.99–1.00 | 0.940 | 1.00 | 0.98–1.03 | 0.962 |
| Alanine aminotransferase | 0.98 | 0.96–1.01 | 0.285 | 0.97 | 0.94–1.04 | 0.714 |
| Aspartate aminotransferase | 0.99 | 0.97–1.01 | 0.682 | 0.99 | 0.92–1.03 | 0.946 |
| Blood urea nitrogen | 0.97 | 0.93–1.01 | 0.214 | 0.98 | 0.91–1.12 | 0.461 |
| Creatinine | 0.63 | 0.47–2.34 | 0.499 | 0.78 | 0.39–6.85 | 0.826 |
| Estimated glomerular filtration rate | 1.00 | 0.98–1.02 | 0.562 | 1.00 | 0.96–1.04 | 0.747 |
| High sensitivity C-reactive protein | 1.47 | 0.93–2.36 | 0.019 | 1.23 | 0.91–4.21 | 0.098 |
| N-terminal pro-B type natriuretic peptide | 1.24 | 0.96–1.71 | 0.034 | 1.17 | 0.94–2.86 | 0.104 |
| White blood cell count | 1.21 | 0.95–1.58 | 0.041 | 1.13 | 0.93–2.44 | 0.137 |
| Neutrophil-to-lymphocyte ratio | 1.01 | 0.75–1.37 | 0.901 | 1.00 | 0.81–2.43 | 0.914 |

CI: Confidence interval; OR: Odds ratio. *Iron deficiency was defined as ferritin <100 mg/L or ferritin 100-300 mg/L and Tsat <20%.

usually associated with an imbalance between inadequate absorption of dietary iron and an increased iron demand or blood loss. Chronic use of oral anticoagulants in AF patients may lead to inadequate intestinal iron absorption and subclinical blood loss from the gastrointestinal tract, resulting in increased frequency of absolute ID. The functional type of ID is primarily caused by hepcidin overproduction due to an inflammatory response, which may again contribute to a higher ratio of ID, especially in permanent AF patients who have a relatively higher hs-CRP level compared with other groups.[19–21] Activation of proinflammatory cytokines in HF blocks intestinal absorption of iron and diverts iron from the circulation to the reticuloendothelial system.[19] AF is also characterized by an increase in proinflammatory mediators. Leukocyte activation has been considered an important potential mediator in the initiation and continuation of AF.[22] Similarly, there is a strong association between CRP elevation and AF persistence.[23] Marcus et al.[24] demonstrated that proinflammatory cytokines activation in AF patients was detected when the patients had

an AF rhythm at the time of the blood draw. They also reported a significant decline in interleukin 6 and CRP levels after catheter ablation in patients with atrial flutter.[25] These findings indicated that inflammation is both a cause and a consequence of AF, which may also explain the higher incidence of ID in patients with permanent AF.

Natriuretic peptides are sensitive biomarkers of cardiac myocardial stretch. Elevation of natriuretic peptides in AF patients is another indicator for the persistence of the arrhythmia.[26] In this study, higher levels of these biomarkers in patients with persistent and permanent AF, and their relative association with ID indicated an underlying subclinical hemodynamic deterioration, which may result in subtle systemic congestion similar to that seen in patients with HF.

## Limitations

The current study has several limitations. First, it was a single-center, retrospective, observational study with a small number of patients, significantly increasing the risk for type I error. Second, the indication for evaluation of ID was at the discretion of the physicians, and therefore the results might have been affected by the selected patient population. Furthermore, as we did not perform bone marrow aspiration, we could not diagnose ID according to the optimal standard. Although we excluded patients with systolic HF and overt clinical signs of HF, there may have been patients with diastolic HF. Finally, due to the retrospective design, we could not demonstrate the patients' comprehensive functional capacity and echocardiographic findings and their relationship to ID.

## Conclusion

ID as defined in HF patients is common in AF patients, especially those with permanent AF, and is associated with inflammatory and neurohumoral activation. Further observational and interventional studies are warranted to investigate the cause, consequences, and possible beneficial effects of correction of ID in these patients.

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## REFERENCES

1. Dunn LL, Suryo Rahmanto Y, Richardson DR. Iron uptake and metabolism in the new millennium. Trends Cell Biol 2007;17:93–100. [CrossRef]
2. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr 2001;131:568S–79.
3. Nemeth E. Iron regulation and erythropoiesis. Curr Opin Hematol 2008;15:169–75. [CrossRef]
4. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet 2007;370:511–20. [CrossRef]
5. Hinton PS, Sinclair LM. Iron supplementation maintains ventilatory threshold and improves energetic efficiency in iron-deficient nonanemic athletes. Eur J Clin Nutr 2007;61:30–9.
6. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361:2436–48. [CrossRef]
7. Haas JD, Brownlie T 4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:676S–88. [CrossRef]
8. Suchdev PS, Williams AM, Mei Z, Flores-Ayala R, Pasricha SR, Rogers LM, et al. Assessment of iron status in settings of inflammation: challenges and potential approaches. Am J Clin Nutr 2017;106:1626S–33. [CrossRef]
9. Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. Eur Heart J 2013;34:816–29. [CrossRef]
10. Çavuşoğlu Y, Altay H, Çetiner M, Güvenç TS, Temizhan A, Ural D, et al. Iron deficiency and anemia in heart failure. Turk Kardiyol Dern Ars 2017;45:1–38.
11. Witte KK, Desilva R, Chattopadhyay S, Ghosh J, Cleland JG, Clark AL. Are hematinic deficiencies the cause of anemia in chronic heart failure? Am Heart J 2004;147:924–30. [CrossRef]
12. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail 2016;18:786–95. [CrossRef]
13. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006;27:949–53. [CrossRef]
14. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962. [CrossRef]
15. Guo Y, Lip GY, Apostolakis S. Inflammatory Biomarkers and Atrial Fibrillation: Potential Role of Inflammatory Pathways in the Pathogenesis of Atrial Fibrillation-induced Thromboem-

bolism. Curr Vasc Pharmacol 2015;13:192–201. [CrossRef]
16. Westenbrink BD, Alings M, Granger CB, Alexander JH, Lopes RD, Hylek EM, et al. Anemia is associated with bleeding and mortality, but not stroke, in patients with atrial fibrillation: Insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Am Heart J 2017;185:140–9. [CrossRef]
17. Lee WH, Hsu PC, Chu CY, Lee HH, Lee MK, Lee CS, et al. Anemia as an Independent Predictor of Adverse Cardiac Outcomes in Patients with Atrial Fibrillation. Int J Med Sci 2015;12:618–24. [CrossRef]
18. Ali AN, Athavale NV, Abdelhafiz AH. Anemia: An Independent Predictor Of Adverse Outcomes In Older Patients With Atrial Fibrillation. J Atr Fibrillation 2016;8:1366.
19. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011–23. [CrossRef]
20. Weiss G. Iron metabolism in the anemia of chronic disease. Biochim Biophys Acta 2009;1790:682–93. [CrossRef]
21. Balla J, Jeney V, Varga Z, Komódi E, Nagy E, Balla G. Iron homeostasis in chronic inflammation. Acta Physiol Hung 2007;94:95–106. [CrossRef]
22. Friedrichs K, Klinke A, Baldus S. Inflammatory pathways underlying atrial fibrillation. Trends Mol Med 2011;17:556–63.
23. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001;104:2886–91. [CrossRef]
24. Marcus GM, Smith LM, Ordovas K, Scheinman MM, Kim AM, Badhwar N, et al. Intracardiac and extracardiac markers of inflammation during atrial fibrillation. Heart Rhythm 2010;7:149–54. [CrossRef]
25. Marcus GM, Smith LM, Glidden DV, Wilson E, McCabe JM, Whiteman D, et al. Markers of inflammation before and after curative ablation of atrial flutter. Heart Rhythm 2008;5:215–21. [CrossRef]
26. Ellinor PT, Low AF, Patton KK, Shea MA, Macrae CA. Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. J Am Coll Cardiol 2005;45:82–6. [CrossRef]

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