Letter to the Editor — Editöre Mektup

Discovering an overlooked fact in atrial fibrillation: Iron deficiency

Dear Editor,

We read the article titled "Iron deficiency and hematinic deficiencies in atrial fibrillation: A new insight into comorbidities" in the current issue with great interest and curiosity.[1] First of all, we would like to congratulate the authors on this novel study. They analyzed an unexamined topic in patients with nonvalvular atrial fibrillation (AF). Despite the similar underlying inflammatory mechanisms and close relationship between heart failure (HF) and AF, previous studies were usually only related to iron deficiency (ID) in patients with HF. A review of the literature review indicated that ID has not previously been evaluated in AF patients, regardless of valvular etiology.

After reviewing the article, we would like to ask some questions about the study. First, what was the objective in defining the ferritin level cut-off points at 100 μg/L? A ferritin level of 30 μg/L and a transferrin saturation of 20% are widely accepted cut-off points for ID. Second, were patients treated with ablation in the past excluded? Patients who had undergone ablation therapy might have had a longer AF-free period, which could affect the underlying inflammatory mechanisms in ID. Finally, intravenous ferric carboxymaltose therapy has been considered quite beneficial in HF.[4] Do the authors think that intravenous and/or enteral iron replacement could be beneficial for the symptoms and functional capacity in patients with AF, as in HF?

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References

1. Keskin M, Ural D, Altay S, Argan O, Börklü EB, Kozan Ö. Iron deficiency and hematinic deficiencies in atrial fibrillation: A new insight into comorbidities. Turk Kardiyol Dern Ars 2018;46:103–10.
2. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 2010;31:1872–80.
3. 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 Mar;45:1–38.
4. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. Eur Heart J 2015;36:657–68.

Authors' reply

Dear Editor,

First, we thank the authors for their kind and important comments. International Nutritional Anemia Consultative Group indicated that at all ages a serum ferritin level of less than 10-12 μg/L is indicative of iron deficiency (ID).[1] These values have been revised in 2011 and a level of 15 μg/L has been considered as reflective of ID.[2] Currently, the generally accepted serum ferritin cut-off level to diagnose absolute ID is <30 μg/L.[3] As ferritin is an acute phase reactant, and nonspecifically elevated in chronic inflammatory diseases, absolute ID is commonly diagnosed with higher cut-off ferritin values (<100 μg/L) and functional ID is diagnosed with normal serum ferritin (100–300 μg/L) and low transferrin saturation (Tsat) (<20%).[4,5] The diagnosis of ID in previous studies with heart failure, which is associated with a chronic inflammatory status, was based on this later definition.[6] As atrial fibrillation is another cardiac disease with increased systemic and local inflammation,[7,8] we used the same cut-off values for ID in our study.

Systemic inflammation may induce atrial fibrillation through several direct and indirect arrhythmogenic triggers, and development of atrial fibrillation may be considered as a consequence of long-term underlying systemic inflammatory triggers. As we aimed to examine a possible relation between systemic inflammation and ID in atrial fibrillation patients, we did not exclude those with a history for catheter ablation to

prevent a selection bias.

Finally, despite having similar underlying mechanisms and close relationships to heart failure, we don't have enough evidence to recommend intravenous ferric carboxymaltose therapy in atrial fibrillation patients without established ID anemia.

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References

1. Preventing and controlling anaemia through primary health care: a guide for health administrators and programme managers. Geneva, World Health Organization, 1989.
2. Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.2).
3. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood 2010;116:4754-61.
4. Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. Clin J Am Soc Nephrol 2006; 1 Suppl 1:S4-8.
5. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood 2010;116:4754-61.
6. 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.
7. Yalta T, Yalta K. Systemic inflammation and arrhythmogenesis: a review of mechanistic and clinical perspectives. Angiology 2018;69:288-296.
8. Cheng T, Wang XF, Hou YT, Zhang L. Correlation between atrial fibrillation, serum amyloid protein A and other inflammatory cytokines. Mol Med Rep 2012;6:581–4.

Iron deficiency and atrial fibrillation

Dear Editor,

We read the article by Keskin et al. about iron deficiency in patients with atrial fibrillation (AF) with great interest. It was reported that iron deficiency was more frequent in patients with AF than in a healthy control group and that iron deficiency and anemia were more common in the permanent AF group.[1]

The major cause of iron deficiency is blood loss; it is most often caused by excessive menstrual bleeding in women of childbearing age and bleeding of the gastrointestinal tract in the remaining population.[2] The main reason for the difference in the prevalence of iron deficiency and anemia between healthy controls and AF patients could be related to anticoagulant medication use or as a result of increased occult bleeding.

Another important point is that medications can affect the absorption and metabolism of iron. There are emerging data suggesting an association between chronic proton pump inhibitor (PPI) use and iron deficiency.[3] Patients treated with anticoagulation more often use a PPI when compared with the normal population. Therefore, we think that PPI use should be taken into account in this study. Additionally, digoxin may affect some genes related to iron metabolism and can cause iron deficiency and anemia.[4] Digoxin use could be another reason for iron deficiency in AF patients.

Finally, the duration of anticoagulation was not assessed. Patients with permanent AF may be under warfarin treatment longer than other groups. This longer duration of anticoagulation may be another reason for the difference in anemia and iron deficiency between the groups.

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References

1. Keskin M, Ural D, Altay S, Argan O, Börklü EB, Kozan Ö. Iron deficiency and hematinic deficiencies in atrial fibrillation: A new insight into comorbidities. Turk Kardiyol Dern Ars 2018;46:103–10.
2. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet 2016;387:907–16.
3. Imai R, Higuchi T, Morimoto M, Koyamada R, Okada S. .Iron Deficiency Anemia Due to the Long-term Use of a Proton Pump Inhibitor. Intern Med 2018;57:899–901.