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Review Article

Iron-Deficiency Anemias Worsen Some Cardiovascular Diseases: The Role of Intravenous Ferric Carboxymaltose

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Abstract

Background: Anemia induced by iron deficiency is a frequent co-morbidity of cardiovascular disease and is called as sideropenic anaemia. This is caused by low iron serum levels, with reduction of the hemoglobin value.

Methods: Iron-deficiency reduces the oxygen carry throughout the body. The reduction of oxygen supply to the cardiac and pulmonary systems can point out some clinical symptoms, such as precordial angor, dyspnea, tachycardia and edema at lower limbs. It also induces an increase of some hemodynamic data, such as pulmonary and capillary pressures and worsens the prognosis of patients subjected to cardiac surgery.

Results: Several data confirm that iron deficiency exerts detrimental effects in patients with coronary artery disease, heart failure, pulmonary hypertension and in those undergoing cardiac surgery.

Conclusions: Iron deficiency further worsen the outcome and the complications of some cardiovascular disease. In addition, the manner and the advantages of i.v. iron administration (ferric carboxymaltose especially) were displayed. This administration may be requested in some conditions of cardiovascular disease and in the coexistence of these with kidney failure.

Keywords: Anaemia; Iron; Coronary artery disease; Heart failure; Pulmonary hypertension; Cardiac surgery; Ferric carboxymaltose

Introduction

Anemia is a very common disease worldwide. It is present in both sexes, particularly in middle aged and elderly subjects [1]. Several causes, such as reduced red blood cells, excessive loss of these (blood dripping), congenital diseases (thalassemia, falciform red blood cells, etc.), or unsatisfactory taking of iron and some B vitamins can induce anaemia [2]. Among these, sideropenic anaemia is the most common form of anaemia and is characterized by a reduction of iron-content in hemoglobin (< 13 gr/dl in men, <12 gr/dl in women) [3].

Anaemia induced by iron deficiency affects up to one-third of the world's population. In many cases, it depends on some pathological/physiological conditions, such as hemorrhagic gastritis, intestinal polypus, bleeding hemorrhoids, chronic renal failure, plentiful menstruations, pregnancy, etc. Loss of the hemoglobin value is unable to supply an adequate amount of oxygen to different organs and systems, with a consequent functional inability of these. Iron metabolism involves two proteins, as transferrin and ferritin. Transferrin is a plasma-protein that transports iron through the blood. In the cytoplasm, iron is employed to synthetize heme-group, cytochromes and others. In contrast, the latter enables iron storage [4].

Sideropenic anaemia clinically shows with paleness, easy weariness, dyspnea for light efforts, coldness and paleness of upper and lower limbs. It also worsens the hemodynamics and symptoms.

Iron deficiency is particularly frequent in patients with some cardiovascular diseases, in whom it is associated with a poor outcome. Particularly, anaemia from iron deficiency can worsen and point out some symptoms induced by asymptomatic chronic Coronary Artery Disease (CAD), chronic heart failure, hypertension of pulmonary system and the prognosis of patients underwent to cardiac surgery [5].

Coronary Artery Disease

CAD happens because of a reduction of coronary lumen-width due to the atherosclerotic plaques, with consequent lowering of blood supply to the myocardial cells. This condition can be responsible of a myocardial ischemia, sometimes displaying abnormal cardiac beats (extrasystolic beats, tachy- or brady-arrhythmias, dyspnea for light efforts, etc.) with or without precordial pain. The contemporary presence of iron deficiency (with or without anaemia) favors a further reduction of coronary blood flow, with reduction of oxygen supply to the myocardial cells (Figure 1). The increase of pre-load (due to the reduced viscosity of the blood), the increase of heart beats and the reduction of stroke volume, further worsen the symptoms of myocardial ischemia when the iron deficiency is present at the same moment [6].

Heart Failure

Iron deficiency is a pathological state often present in patients with chronic heart failure (Figure 2). In which it is predictive of increased morbidity and mortality. Iron deficiency in people with chronic heart failure (prevalently diastolic heart failure) is estimated around 30-50% and mainly present in women. A suitable iron serum concentration comes from the role of hemoglobin in the oxygen transport, from

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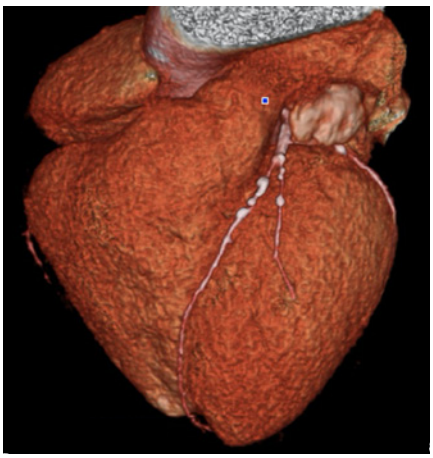

Figure 1: Coronary-CT angiography - Reduction of coronary lumen in a patient with asymptomatic CAD.

Figure 2: Chest X-ray in AP projection - Increase of the cardiac silhouette for chronic heart failure.

iron value in the myoglobin composition (iron is present in 10-15%) and from iron function in the composition of respiratory chain. Therefore, iron-deficiency is responsible for the reduction of physical activity, the impairment of cognitive performance, and the compromise of behavior and emotions [7]. Therapeutically, after the inefficiency of oral iron supply in the improvement of symptoms of heart failure pointed out in IRONOUT study [8], FAIR-HF study [9], CONFIRM-HF study [10], and EFFECT-HF trial [11] highlighted that i.v. iron giving as ferric carboxymaltose is able to improve the degree of anaemia, the NYHA functional class and the physical activity of patients with heart failure.

Pulmonary Hypertension

Pulmonary hypertension is a disease with unfavorable prognosis. With reference to its etiology, pulmonary hypertension is divided in primary (idiopathic) and secondary form. Hemodynamically, pulmonary hypertension is characterized by an increase of pressure in common pulmonary artery, in its two branches and in pulmonary capillaries (wedge pressure). These increased values of pulmonary pressure are usually complicated by the reduction of cardiac output and right ventricle dilation (Figure 3). A recent study pointed out that a protein (responsible for iron deficiency) is often present in primary

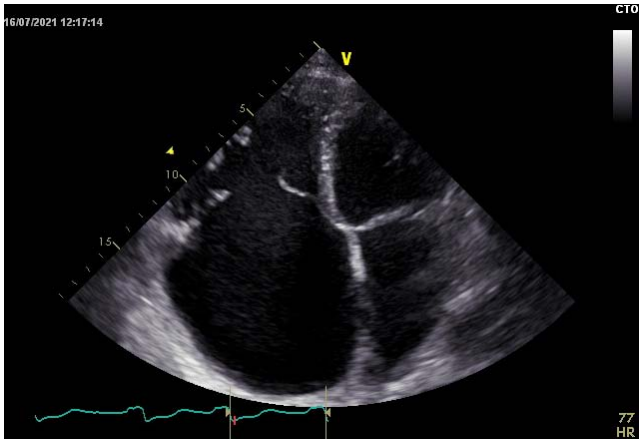

Figure 3: 2D-Trans-thoracic Echocardiography - Right cavities dilation in a case of pulmonary arterial hypertension.

Table 1: The main states compelling the injection i.v. iron.

Leading conditions requiring i.v. iron
Severe anaemia due to iron-deficiency
Intolerance to oral iron
Decreased intestinal iron absorption
Functional iron deficiency
Anaemia of inflammatory diseases
Anaemia of kidney disease
Anaemia of cancer
Other conditions

(idiopathic) pulmonary arterial hypertension only [12]. The normal amount of hematic iron (hemoglobin) is important to supply oxygen to the organs and the tissues. Therefore, the transfer and the spread of a suitable amount of oxygen to the muscular and other districts is difficult and inadequate in the presence of pulmonary hypertension and iron deficiency simultaneously. Finally, i.v. iron administration is the most effective method to reduce the degree of sideropenic anemia, to increase the length of physical activity and improve the hemodynamic parameters in pulmonary hypertension [13].

Cardiac Surgery

Sideropenic anaemia is a frequent complication of the patients requiring cardiac surgery. That induces a prolonged hospitalization, a significant increase of morbidity (including renal complications) and mortality and a greater length of mechanical ventilation (Figure 4). Particularly, the i.v. iron supplement significantly improves some parameters, such as red blood cells, hemoglobin value, ferritin, and others. Some AAs recently reported that a whole of iron, erythropoietin, vitamin B12 and folic acid, supplied to the heart surgery patients a day before the surgical intervention, allows to reduce the number of blood transfusions [14,15].

Ferric Carboxymaltose

Referring to the re-integrability of iron-deficiency, contrarily to the oral therapy, the i.v. iron administration is quickly effective [16]. Oral iron formulation has the advantage to be cheap, but is

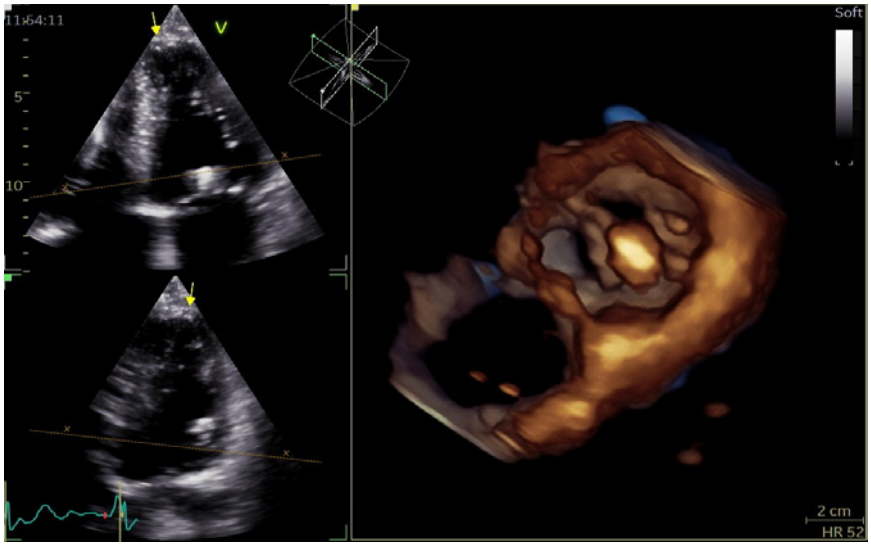

Figure 4: (left) 2D-Echocardiography in a patient subjected to mitraclip. (Right)-3D-Echocardiography of the mitral and tricuspid rings in the same patient.

limited by poor compliance, poor absorption and low efficacy. On the contrary, i.v. iron treatment presents some advantages, such as faster and higher increase of Hb and rapid body replenishment of iron. Markers indicating a need of i.v. iron include a ferritin less than 100 μ/L, a transferrin saturation less than 20% and a percentage of hypocromic red cells more than 10% [17]. The different i.v. iron formulations are: iron dextran, iron gluconate, iron sucrose, ferric carboxymaltose. Among these, ferric carboxymaltose is a compound with better safety profile and usually employed [18]. It is a complex of a ferric hydroxide and carbohydrate shell that rapidly improves hemoglobin levels. The medication is usually given in two doses, mostly 7 days apart. Intravenous infusion happens in a short time (15-20 min.) A single dose of the drug consists of 750 mg of iron in the US and 1.000 mg of iron in Europe. Rarely, the drug can induce some negative effects, as anaphylactic reaction, therefore its administration must be exclusively performed in a medical environment. After its administration, ferric carboxymaltose is distributed to the bone marrow, liver and spleen and replenishes depleted iron-stores, including ferritin and transferrin [19,20].

In FAIR-HF and CONFIRM-HF studies, ferric carboxymaltose demonstrated to be able to decrease NYHA functional class and exercise capacity in chronic heart failure [9,10]. But, it corrects iron-deficiency anaemia in other populations also, including patients with chronic kidney disease, nutritional anaemia, gastro-intestinal bleeding, inflammatory bowel disease, post-operative bleeding, heavy uterine bleeding, post-partum iron deficiency and others [21].

The coexistence of some cardiovascular disease and Chronic Kidney Disease (CKD) frequently occurs. This condition usually requires the i.v. iron administration (Table 1). That depends by a state of negative iron balance. That derives from hemodialysis and insufficient iron absorption due to the upregulation of hepcidin secondary to the inflammatory state. These patients usually are treated with an erythropoies-stimulating agent and i.v. iron compound, usually ferric carboxymaltose [22].

Conclusive Remarks

Iron deficiency, with or without anaemia, frequently (20-30%) coexists with CAD and worsens the symptoms and the prognosis of cardiovascular diseases. Particularly, sideropenic anaemia acts on asymptomatic CAD, displaying anginal pain at rest or during effort and/or other symptoms (dyspnea, distress, throbbing, etc.) [23]. On the contrary, in a recent study, Gill et al. of the Imperial College of London demonstrated that the correction of iron deficiency in CAD is associated with a reduction of the symptoms of CAD [24]. The adjustment of iron deficiency in chronic heart failure causes an increase of the hemoglobin value, improving tissues' oxygenation, myoglobin formation and production of the enzymes of respiratory chain [26]. Iron deficiency is also correlated with pulmonary artery hypertension (idiopathic form specially), worsening the prognosis [25]. Finally, the i.v. correction of iron deficiency in anaemic patients requiring an intervention of cardiac surgery improves the prognosis because favors ATP generation, preserves normal mitochondrial working and maintains normal DNA metabolism [27].

Conclusively, the anaemia by iron-deficiency is a nutritional disorder, commonly found in some cardiovascular disease. In these patients, it exerts a negative impact because worsens their symptoms and increases the morbidity and mortality. Its etiology in cardiovascular disease is barely known, even if the inflammation seems to have a role.

Therapeutically, oral iron supplementation had a limited success. On the contrary, ferric carboxymaltose or other intravenously used compounds (as iron sucrose) have a clear benefit after few administrations performed in a little time [28].

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