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Review Article

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Clinical implications of iron deficiency in heart failure, an approach to the treatment

José Ildefonzo Arocha Rodulfo[1], Trina Navas Blanco[2], Pablo Amair M.[3], Rusvel Gómez Berroterán[4]

[1]Cardiologist, Chapter of Arterial Hypertension, Venezuelan Society of Cardiology, Venezuela.

[2]internist, graduate of Internal Medicine, General Hospital West "Dr. Jose Gregorio Hernandez", the Magallanes, Venezuela.

[3]Doctor nephrologist, Chapter Cardiorenal, Venezuelan Society of Cardiology.

[4]Cardiologist, Hospital "Domingo Luciani", Caracas, Venezuela.

Clinical implications of iron deficiency/anemia in heart failure and approach to the treatment

Abstract

An important comorbidity recognized increasingly in patients with heart failure (HF) is iron deficiency with or without anemia. Although iron deficiency is easily diagnosed by means of two biomarkers, (serum ferritin and transferrin saturation) it is underdiagnosed in patients with heart failure and might affect 50% of those patients. Even before the start of the anemia, physical and cognitive performance with a poor quality of life is evident in patients with heart failure HF and iron deficiency. Moreover, iron deficiency is risk factor independent of anemia, of unfavorable progression (death or heart transplant) in patients with chronic heart failure HF. Several randomized controlled studies performed by the New York Heart Association (NYHA) have shown improvement in exercise capacity and functional class; improving the quality of life after iron deficiency treatment. Several factors contribute to the development of this iron deficit, including advanced age, kidney failure, hemo-dilution, chronic inflammation and heart failure severity. A variety of postulated mechanisms have gained great attention to explain the relationship between iron deficiency and heart failure as a therapeutic target in these patients.

Keywords: Iron deficiency, anemia, ferritin, heart failure (MeSHsource).

Implicaciones clínicas de la deficiencia de hierro en la insuficiencia cardíaca y abordaje del tratamiento

Resumen

El déficit de hierro con o sin anemia está siendo reconocido cada vez más como una comorbilidad importante en los pacientes con insuficiencia cardíaca (IC). Aunque la deficiencia de hierro es fácilmente diagnosticada por medio de dos marcadores (ferritina sérica y saturación de transferrina), es subdiagnosticada en estos pacientes y pudiera afectar hasta el 50% de los mismos. Aun antes del inicio de la anemia, los pacientes con IC

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e-mail address : jiarocha@gmail.com

y déficit de hierro muestran disminución en el rendimiento físico y cognitivo, con una mala calidad de vida. Más aún, la deficiencia de hierro es un factor de riesgo, independiente de la anemia, de evolución desfavorable (muerte o trasplante cardíaco) en los pacientes con IC crónica. Varios estudios aleatorios controlados han mostrado mejoría en la capacidad de ejercicio, clase funcional de la New York Heart Association (NYHA) y calidad de vida, luego de la corrección del déficit de hierro. Diversos factores contribuyen al desarrollo de este déficit, incluyendo edad avanzada, falla renal, hemodilución, inflamación crónica y severidad de la IC. Una variedad de mecanismos se han postulado para explicar la asociación de déficit de hierro e IC, y su corrección, como un blanco terapéutico, está ganando una mayor atención.

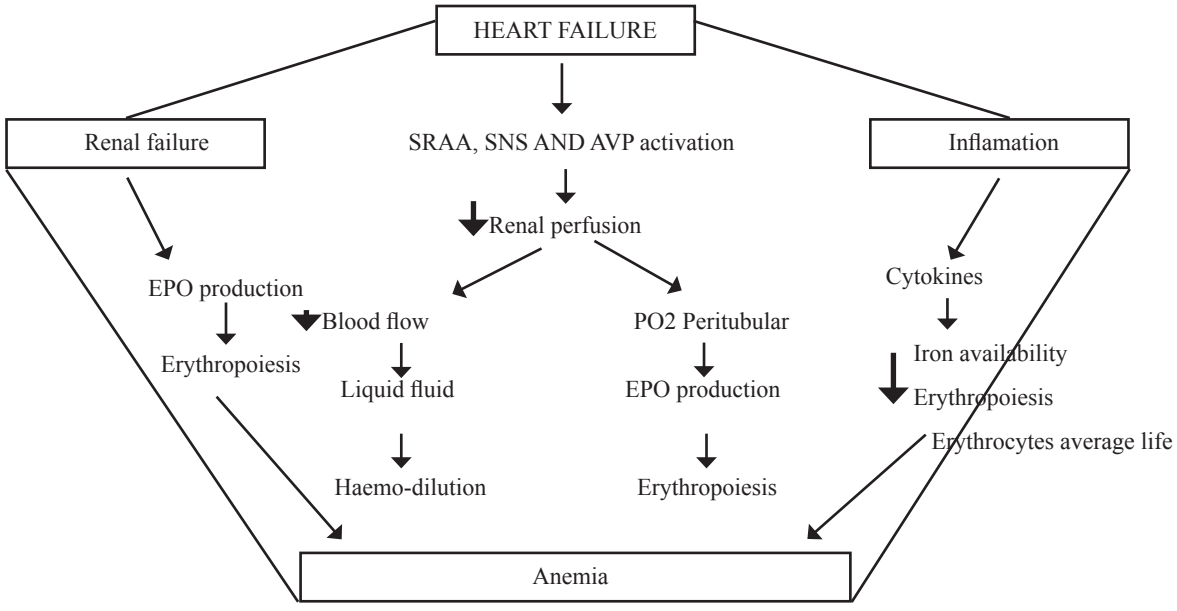
Palabras clave: Deficiencia de hierro, anemia, ferritina, insuficiencia cardíaca (fuente DeCS).

Introduction

Progress has been achieved in understanding the pathophysiology and progression of heart failure (HF) in the last two decades due to the recognition of a series of neuro-hormonal, immunological and metabolic abnormalities that took place during the natural history of anemia and renal failure, among them leading to adverse outcomes. The emergence of the Cardio renal-Anemia Syndrome(CRAS, its English acronym) is no more than a representation of a menage a trois perverse, where the failure of a single organ - either the heart or kidney- leads to the deterioration in the function of the other[1]. Further, the presence of anemia or kidney failure increases morbidity and mortality in patients with heart failure, suggesting that there is a malfunction in the defense mechanisms built into the process of the HF, Chronic Kidney Disease (CKD) and

Figure 1

Relationship between anemia, kidney failure and heart failure: possible mechanisms for reduction and deterioration in erythropoietin production



Abbreviations: EPO: Erythropoietin; PO2: partial pressure of oxygen; SRAA: renin angiotensin aldosterone; SNS: sympathetic nervous system; AVP: arginine-vasopressin.

anemia (Figure 1), where each of these actors might aggravate the condition of the other one[2]. Therefore, treating anemia or iron deficiency is a primary factor needed to modify the severity and prognosis of the heart failure. This is because of the main role iron plays in a series of mechanisms that will be discussed later.

Therefore, it is imposed in patient management with HF, in addition to the clinical control and functional class, the strict monitoring of the cardiac function (by two-dimensional echocardiography and the determination of the atrial natriuretic peptide) renal function monitoring (estimated glomerular filtration rate, EGFR) and the hematological variables (especially ferritin and saturation, or determining hemoglobin in case of not having the previous two).

Iron deficiency versus anemia as predictor variables

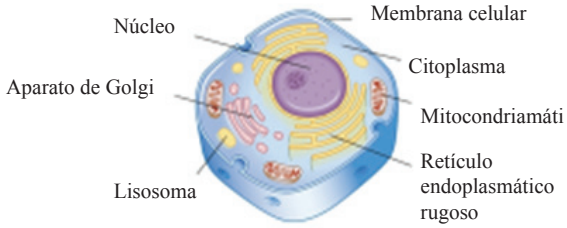
The most common nutritional failure throughout the world is iron deficiency which affects more than one third of the population. Although this deficit, is related to the anemia; Iron deficiency is more prevalent than anemia, with serious economic consequences, besides being unnoticed in most of cases. Iron deficiency affects the human role and limits organisms survival at any level of complexity; its fails, are expressed in various alterations in human being, summarized below:

Based on World Health Organizations[6], anemia was considered as the values of hemoglobin <13 g/L, in men, and <12 g/L, in women. Therefore, the most powerful predictor variable according to a series of published studies based on observations and by the belief that iron was essential to hemoglobin production or a component of hemoglobin responsible for binding oxygen. Nevertheless, two recent discoveries changed this concept; in this paradigm[3,4,7]:

1. The discovery of the hepcidin system-ferroportin: The first is a polypeptide of 25 amino acids hormone that formed mainly in the liver and

Figure 2

Iron deficiency's impact on human being function and survival [3-5]



- Mitochondrial dysfunction
- Enzyme activity disruption
- Estructural abnormalities and protein transport
- Apoptosis

- Tissue remodeling
- Deterioration of Organs function

- Impairment of Exercise capacity
- Reduction of working efficiency
- Deterioration of cognitive performance
- Increased morbidity and mortality.

whose target is ferroportin; this one is considered as a transporter whose function is to remove the iron out of the cell. This iron exporter is a transmembrane protein founding all body tissues that mobilize iron. In these cells, iron export is proportional to the ferroportin concentration. Hepcidin is an iron regulator while Ferroportin is the actual receptor which transport in and out of a cell and when hepcidin binds to the receptor, it causes an internalization and intracellular degradation, reducing its appearance in the membrane and therefore the cells' ability to export iron as well.

2. The knowledge related to Iron metabolic functions, due to many bio-molecules, as myoglobin, cytochromes and some enzymes require iron to be active metabolically

Iron deficiency was labeled clinically as relevant, in relation with anemia traditionally. However, the current and prevailing point of view is to consider the anemia, as the end of a process that began much earlier, with the gradual depletion of iron deposits shown in the physical capacity and tolerance to daily activities[7].

In other words, anyone is at risk of iron deficiency anemia.

Iron deficiency anemia/in heart failure

Anemia as comorbidity is often in chronic condition associated with heart failure HF Its incidence and prevalence have been studied in retrospective analysis, based on Studies of Left Ventricular Dysfunction (SOLVD) test[8].In this test only 18.4% of attendees were carriers of anemia and this percentage is increased by 9.6%, additionally, in the first year of study. In Valsartan in Heart Failure Trial (Val-Heft)[9], the prevalent result at time of patient admission was 23% and new emergent anemia during the study was observed in 16.9% of the participants; even more, there was a lower occurrence of events in those patients with anemia, or not, that had increased in hemoglobin concentration. In the study carvedilol or Metoprolol European Trial (COMET)[10], 15.9% of the patients were diagnosed with anemia upon their admission and 14.2% of the participants developed anemia during the first year of observation. After five years of monitoring, the new emergent anemia was diagnosed in 27.5% of the studied population. During the observation process, total mortality, death or hospitalization and hospitalization for heart failure HF was significantly higher ($p<0.0001$ for each variable) in patients with anemia compared to those without anemia.

In Groenveld and collaborators meta-analysis[11], 153 - 180 patients with heart failure HF were included, reported in 34 studies published between 2001 and 2007, the prevalence of anemia was calculated from 37.2% (10-49%); a similar amount in the registry Study of Anemia in Heart Failure Population (STAMINA-HFP)[12], with 34% was registered.

It is necessary to take into account that the variability and prevalence in the estimated figures is partially attributed to different definitions of anemia, so that patients with heart failure HF in a decompensated acute phase suffer more anemia by dilution increasing the prevalence.

Patients with heart failure HF and anemia tend to be older than their non-anemic pairs[13]; in addition, below 55 years old, there is no difference in the incidence of anemia[14].

In relation to the status of the systolic function, a large proportion of the trials of prevalence have been practiced in populations with reduced systolic function. Based on SENIORS[15] survey data , in patients with HF and preserved systolic function, noteworthy the small proportion of patients with anemia (10%) showed a greater risk of reaching a primary endpoint and after adjustment by multiple variables, the figure of hemoglobin remained as an independent variable of primary outcomes in this cohort (HR 0.94 per increment of 1 g/dL, 95% CI 0,89-0,99, P= 0.017).

The updated guidelines 1617 for HF treatment recognize that iron deficiency is a common comorbidity and clinically relevant in the management of these patients, associated with a further deterioration in the functional capacity. Regardless of the presence of anemia the quality of life and mortality is highest, for this reason, its treatment should be considered as an attractive therapeutic objective. However, the shortage of solid evidence to confirm the benefit of

iron restitution is not available at this time.

Pathophysiology of iron deficiency anemia in the HF

It is important to consider that it is a multifactorial entity, where various mechanisms overlap one another with greater participation, according to the underlying alterations.

In this regard, and concisely, several factors have been involved, as [3-5,7.18]:

a. Inhibition of endogenous erythropoietin synthesis.

b. Resulting from inhibitors of the renin-angiotensin system therapy (ACEI or BRA), the evidence is circumstantial, although this aspect is highly questionable.

c. Deterioration in the production of erythropoietin secondary to damage or renal failure.

d. Haemodilution.

e. Functional iron deficiency and/or absolute iron.

f. Deteriorate. The restriction of physical activity. The restriction of physical activity in the absorption and/or metabolism of vitamin B12 and folate.

g. Inflammatory cytokines increasing, especially the tumor necrosis factor alpha and interleukin-6, which is known to suppress erythropoiesis and interfere with the action of erythropoietin, suggesting that the occurrence of deterioration in the response to the bone marrow is by the action of these cytokines, regardless of high levels of erythropoietin in blood.

Consequences of Iron Deficiency

Three fundamental aspects are modified by the iron deficiency in patients with heart failure HF:

a. Quality of life. Patients with heart failure HF, suffer commonly a significant deterioration in their quality of life related to health, taking as a reference the multidimensional parameters of Health-Related Quality of Life (HRQoL and Well-Being according to its acronym in English), compared with others with chronic conditions, mainly due to limitations in carrying daily life activities out. In a European and transversal study, 1278 patients with HF were sampled , iron deficiency had a negative impact on HRQL, regardless of the anemia[19]. In this study, 58% of the patients had iron deficiency and 35% had anemia. The HRQoL (measured using the Minnesota questionnaire living with HF) in patients with iron deficiency, with anemia was worse, compared with those ones without iron deficiency or without anemia (score not overall adjusted 42±25 vs. 37±25 for absence of iron deficiency, $p<0.001$; patients with anemia 46±25 vs. 37±25 in patients without anemia $p<0.001$). This difference remained independent from hemoglobin. The above data suggests these new concepts, because these ones propose, despite having normal figures of hemoglobin and hematocrit, to assess iron deposits and metabolism to optimize the patient quality of life .

b. Physical capacity. Physical activity together with quality of life deterioration and increased morbidity and mortality are symptoms and cardinal signs in heart failure HF patients. Where iron is present the exercise tolerance is reduced in various chronic conditions. In a study with 443 patients with HF sampled and the ejection fraction less than 45%, these ones were submitted to cardiopulmonary effort assessment[20]. 155 of them (35%) had iron deficiency-. compared to the control group, a peak of oxygen consumption (VO2) lower (15.3 and 13.3, respectively, $p<0.05$) and increased slope VE-VCO2 (50.9 and 43.1, respectively, $p<0.05$) was shown. The iron deficiency showed an independent relationship and inverse to the VO2 max (including when the presence of anemia is controlled).

c. Survival. Based on several studies it is revealed that iron deficiency, but not the anemia in patients with HF, acute or chronic, is independently associated with mortality[21,22].

As a consequence, it is necessary to postulate both entities separately, considering the chronology the essential factor, where iron deficiency emerge first,

which then becomes a more complex syndrome capitalized by the anemia.

Iron deficiency definition

Iron deficiency has been categorized as absolute or functional, and anemia occurs when such failure is severe enough to reduce the erythropoiesis and decrease the production of hemoglobin[3,5,23]. The absolute deficiency of iron occurs when the deposits are depleted, although iron homeostasis is intact and the gold standard for its diagnosis is the absence of iron in bone marrow smear, tinged with specific stains as Prussian Blue[23]. However, it has been found that the determination of serum ferritin is a faithful reflection of the iron deposit in the bone marrow and the reference values for the diagnosis of iron deficiency are between <15 to 30 µg/L, taking into account that ferritin is a positive acute phase protein and its values increase in stable chronic inflammation situations, despite depleted iron deposits in the bone marrow[23].

A functional deficit is considered when the iron supply is inadequate to provide iron demands and it has been established as <20% of the cut off point for saturation transferring, (Tsat by its abbreviation in Spanish), as this is an iron reflection currently available[23].

However, as well as Fitzsimons and Doughty established[23] in their interesting publication, "there is not a perfect procedure for the diagnosis of iron deficiency". Based on a pragmatic point of view, it is recommended the procedure normally used in clinical studies. Iron deficiency is defined as a ferritin level <100 µg/L or a normal value of ferritin (100 to 300 µg/L) with a Tsat <20%.

- Functional iron deficiency is more common in the early stages of the heart failure HF, progressed to an absolute deficit in the way the syndrome advances.

Iron deficiency treatment in patients with heart failure HF

Despite having studies that show benefits for anemia treatments in patients with heart failure, such as the use of parenteral iron, both the updated European and American guidelines[16,17] do not consider these treatments (parenteral iron and EPO) relevant taking into account that the therapeutic options do not have the support of controlled studies on clinical endpoints strengths. However, based on American College of Physicians, published in 2013[24], where the recommendations for anemia treatment in HF patients, suggest that although the use of transfusions and erythropoiesis stimulate agents are not recommended, the use of parenteral iron may be a possibility.

Therefore, the recommendation for anemia treatment in HF patients is still controversial. Although some experiments show a beneficial effect in the use of parenteral iron in relation with quality of life, through the improvement of the exercise, taking into account that anemia is a condition that adversely modifies the HF prognosis, it should be treated using the available resources, without infringing upon the stability of the patient, reasoning in terms of time and way to treat individually [16].

The erythropoiesis stimulating agents (ESA), which include the natural erythropoietin and synthetic, from the first to the next generation, were consolidated as an effective treatment in the anemia of the ERC and cancer, although there has emerged some concerns with regard to its security, particularly when these are entitled to high levels of hemoglobin[25,26]. However, the benefit of these drugs on quality of life of these chronic diseases patients is well documented. In the case of HF patients, the ESA has been evaluated in several, but controlled studies, using a variety of formulations and recommended dose with a global benefit on hospitalization; and in two meta-analyzes[27,28], published in 2010, which showed that patients treated with ESA showed a significant increase in the quality of life, exercise tolerance and decline in the class of the NYHA, along with a lower risk of hospitalization for HF, without an increase in mortality or adverse events compared with the placebo group.

However, two controlled studies[29,30], the prior with no more than 300 patients, and the latter with 2728 and 28 months of monitoring, giving as a result that there is no a significant difference between the treatment with alpha erythropoietin synthetic (Second

Generation) or placebo, in addition to the increased risk demonstration of the of cerebrovascular events in this group of patients[31]. With them the chapter of possible therapeutic usefulness of the ESA in HF is closed

Administration of iron in patients with IC

In most of the cases, oral iron supplementation has been the first choice in iron deficiency treatment, due to its effectiveness and low cost. Unfortunately, there are many chronic conditions where the oral administration is less than ideal, particularly due to the gastrointestinal adverse events and the long time required to reach the ideal values of hemoglobin and saturating deposits of body iron deposits [32].

The first product of iron for intravenous use (IU) was dextran of high molecular weight, which did not gain acceptance, due to the high risk of anaphylactic reactions. At the beginning of this century, there were two new preparations to be provided by mouth: the ferrous gluconate and the sacarato, as safer alternatives to iron dextran. In the last decade, other formulations have been developed and put in the market (carboxymaltose, isomalt and ferumoxytol) safer than the traditional intravenous compounds and with more promising results in relation to a rapid saturation of iron deposits (15 to 60 minutes/infusion), because higher doses can be administered (from 500 mg to more than 1000 mg/infusion)[32,33].

Initially, iron supply via IU was evaluated in several exploratory tests, with a small number of patients and short monitoring process[34,35]. In these cases, its IV supply caused a remarkable increase in the concentration of hemoglobin, accompanied by an improvement in the remodeling of the left ventricle, exercise tolerance and in the functional category of the NYHA.

These exploratory analyzes were followed by studies of best design (double-blind, randomized and prospective), with a greater time of monitoring and using end points surrogates, as listed below[36-40]:

- Tobli and collaborators study[36], a prospective, randomized, double-blind and placebo-controlled analysis was conducted based on the effect of iron sacarato (five doses of 200 mg/week), in comparison to the supply of isotonic saline solution as a placebo in 40 patients with HF (FE≤35%), anemia, iron deficiency (ferritin <100 mg/L and/or transferrin saturation <20%) and mild renal impairment. The trace is fulfilled by six months. Compared with the placebo arm, the administration of iron by mouth increased significantly, hemoglobin and parameters related to the determination of iron. Further, the NT-proBNP and C-reactive protein decreased significantly ($p<0.01$ for both variables). In the group treated with iron occurred a significant improvement in the NYHA functional class, in the Minnesota score of living with HF (MLHF) and in the distance walked in the test of the 6 minutes ($p<0.01$ for all).
- Ferric iron sucrose in Heart Failure (ferric-HF)37, conducting randomized, controlled and with blind end points study, included 35 patients with HF (class II-III of the NYHA) with iron deficiency and were assigned randomly to receive, for 16 weeks, iron sacarato EV (200 mg/week for 3 weeks, followed by 200 mg at weeks 4, 8, 12 and 16) or placebo in a ratio 2:1. Compared with the placebo group, there was no significant increase in the absolute peak of the oxygen uptake (pVO2) (95% CI 12 to 205 mL/min; $p=0.08$) in the group treated with iron IV. However, when pV02 was adjusted according to body weight, (pVO2) increased significantly, in the group of patients who received iron (95% CI 0.5 to 4 mL/kg/min; $p=0.01$).
- Ferinject Assessment in Patients with iron deficiency and Chronic Heart Failure (FAIR-HF)[38], conducting a multicenter, prospective, double-blind, randomized, placebo-controlled study, was designed to compare the administration of Ferric Carboxymaltose IV (CMF) in patients with HF and iron deficiency, with or without anemia. 459 patients were admitted and were distributed in a 2:1 ratio: 304 received CMF at the dose of 200 mg weekly until iron deposits were replete and 155 treated with placebo. The administration of iron by mouth, compared to treatment with placebo, increased significantly

serum ferritin and hemoglobin levels by week 24 (p<0.001). For the primary end point in week 24, 50% of the participants by applying iron into the arm EV reported improvement in the scale for the overall evaluation of the patient, compared to 28% in the placebo group (odds ratio; 2.51; 95% CI, 1.75 to 3.61; P<0.001). Similarly, 47% of the patients who received iron showed improvement in the NYHA functional class, compared to 30% in the placebo group (odds ratio 2.40, 95% CI 1.55 to 3.71; P< 0.001). With regard to the secondary end points, walking distance to the 6 minutes and the score on KCCQ scale (for Kansas City Cardiomyopathy Questionnaire), by week24 patients showed a significant improvement in response to treatment: half of the effect in the walk test 35±8 m and at +7 points on the scale KCCQ (p<0.001 for both variables). In a previous defined subgroup, the magnitude of the treatment was not different in subjects with or without anemia at baseline, even when the haemoglobin values did not change in the group of subjects non anemic, in comparison to the placebo group. The overall rate of adverse events was similar in both groups, but the frequency of the first hospitalization for cardiovascular events was lower in those treated with iron, compared to those who received a placebo (hazard ratio, 0.53; 95% CI 0.25 to 1.09; p=0.08).

In a subsequent analysis designed to investigate the effects of iron EV on renal function and the efficacy and safety of this therapy in patients with renal failure39, the results showed that in comparison with placebo, treatment with CMF was associated with a substantial increase from the fourth week, and being statistically significant in week 24 (p=0.039). This effect was observed in all subgroups defaults. The safety profile and adverse events was similar in both treatment groups.

- The test CONFIRM HF (Ferric Carboxy¬maltose evaluation on performance in patients with iron deficiency in combination with chronic Heart Failure) 40, under a design double-blind, placebo-controlled study, 304 patients with symptomatic HF and stable condition in 41 centers in 9 European countries and levels of serum ferritin below 100 ng/mL or between 100 and 300 ng/mL, if transferrin saturation was less than 20%.

  The patients were assigned to receive iron EV (n=152), based on the form of solution of CMF or placebo (n=152) by 52 weeks. At baseline, required the implementation of a complete test of hike of 6 minutes (PC6M) and the primary end point was the improvement in such proof in week number 24. As secondary end points, changes were incorporated in the class of NYHA, overall assessment of patient (OAP), distance in the PC6M, quality of life, score of fatigue to the weeks 6, 12, 24, 36 and 52, and the effect of the CMF on the rate of hospitalization due to worsening of the IC. In the results of the CMF arm, the average total dose was 1500 mg of iron during the year of study (ranging from 500 to 3500 mg). More than 75% of the patients required a maximum of two injections of CMF to correct and maintain the parameters of serum iron.

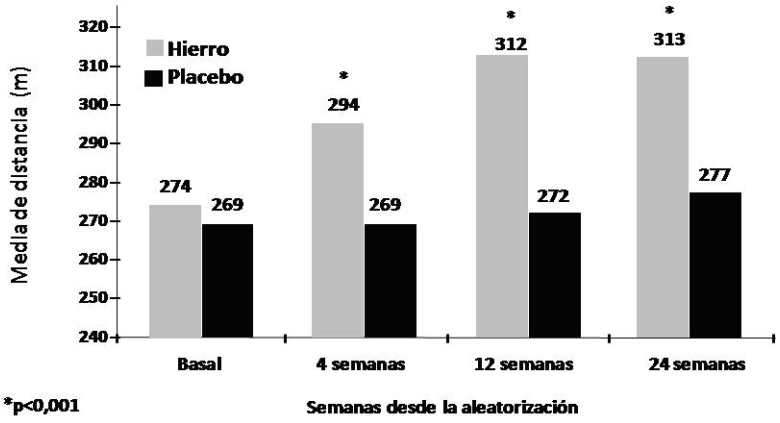
The treatment with CMF lasted, significantly, the distance in the PC6M at week 24 (difference versus placebo: 33 ± 11 meters, p=0.002), being consistent in all subgroups and sustained until week 52 (difference versus placebo: 36 ± 11 meters, p<0.001), as shown in Figure 3.

A significant improvement since week number 24 was obtained, in the NYHA class, EGP, quality of life and score of fatigue, in those ones attended with CMF. Equally, there was a significant reduction in the risk of hospitalization due to worsening of the HF (HR 0.39 [95% CI 0.19-0.82], p= 0.009), results can be observed in Figure 4. The number of deaths (CPM: 12 and placebo: 14) and the incidence of adverse events were comparable between the two groups.

In short, the magnitude of the treatment effect with CPM ON THE PC6M is solid and clinically significant, comparable to that obtained with the cardiac resynchronization therapy and the improvement in the distance walked was observed in all subgroups, including the participants with and without anemia.

Figure 3

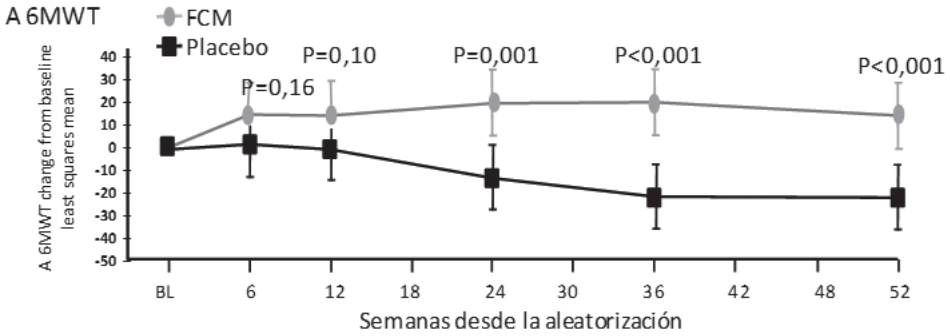
Distancia caminada en el estudio FAIR - HF



Modificado de Anker SD et al. N Engl J Med 2009;361:2436–48.

Figure 4

CONFIRM-HF study. Six minutes walk test



FCM					
No de pacientes	143	137	130	122	125
LS mean (IC 95%)	14 (0,28)	15 (1,29)	19 (5,34)	20 (5, 34)	14 (-1,29)
Placebo					
No de pacientes	148	146	131	123	121
LS mean (IC 95%)	1(-13,14)	-1 (-15,12)	-14 (-28,1)	-22 (-37, -8)	(-22 (-37, -7)
FCM vs Placebo	14 (-5,33)	16 (-3, 35)	33 (13, 53)	42 (21, 62)	36 (16,57)

Modificado de Ponikowski P et al. Eur Heart J 2015;36:657–68

To finish, Qian and collaborators[41], which included studies published until December 2014, with a total of 907 patients sampled, showed that iron supplementation reduced the risk of: (a) hospitalization for HF, and (b) the combined end point of hospitalization for HF and death significantly, without increasing the risk of adverse events in patients with systolic HF symptomatic and iron deficiency.

Another meta-analysis published by Jankowska and collaborators42, with 509 patients sampled treated with iron EV and 342 controls, showed that with the iron therapy, a reduction of 56% in the risk of end points of total mortality or cardiovascular hospitalization (OR 0.44; 95% CI 0.30 to 0.64; $p < 0.0001$), and the end point of cardiovascular related death with hospitalization due to worsening of the IC (OR 0.39; 95% CI 0.24 to 0.63; $p = 0.0001$), in addition to the improvement in the functional class NYHA, walking distance and quality of life.

The correction of the deficit of iron as a target in the patient with HF

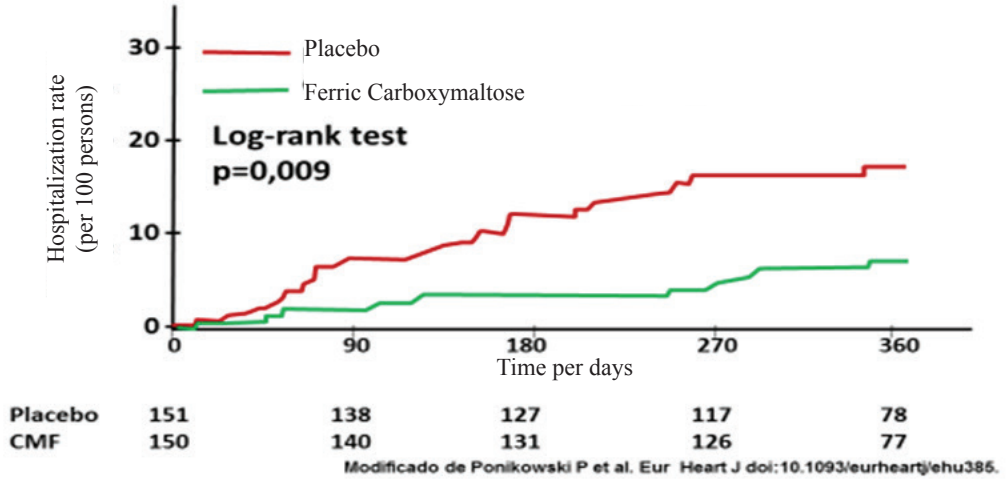
These results of the clinical studies lead to a consistent signal in improving the ability to exercise and quality of life in response to IV treatment with iron in patients with HF and iron deficiency. In most of these trials, the improvement of symptoms with the therapy is accompanied by an increase in the figures of hemoglobin.

It is assumed that the responsible mechanism for the clinical benefit of the refitting parenteral of iron is the increase in the supply of oxygen to the tissues associated with the increase of the hemoglobin[43]. However, the findings reported in the subgroup of patients without anemia of the study FAIR-HF suggest that other routes may be involved, since this group of patients showed a significant improvement in the functional capacity, without substantial changes in the concentration of hemoglobin in response to IV therapy with iron[44].

In HF the reduction of the reserve of the cardiac output, the deterioration of the regulation of the flow to skeletal muscle, and abnormalities in the muscle mass and its metabolism, seem to be crucial factors in the pathophysiology of intolerance to physical activity[23]. Many of the main proteins responsible for oxygen transport and transfer (hemoglobin, myoglobin, guanililcyclase) and its use in the skeletal muscle (cytochromes and enzymes with iron sulfide

Figure 5

Confirm – hp study Time in relation with first hospitalization due to aggravation of heart failure



involved in the transport of oxygen in the mitochondria) require iron as an essential component for normal enzymatic activity[3,45].

The effects of iron deficiency on the metabolism of the skeletal muscle and performance with exercise have been extensively researched46. In rats with diet low in iron, iron deficiency was developed within a few weeks and was associated with proportional reductions in hemoglobin and the cytochromes of skeletal muscle containing iron. In animal samples with iron deficiency, the transfusion of exchange enabled the researchers to evaluate the independent effects of the failure of iron while maintaining, experimentally, the control of the figure of hemoglobin. In these studies the performance depended on exercise increased in direct proportion to the increase in the concentration of hemoglobin in rats with good level of iron, but not in those with deficiency. A comparable pattern of response was observed in isolated limb perfusion that allowed a precise control of the supply of oxygen to the skeletal muscle. These findings suggest that the dependent changes of iron in the use of the substrate in the muscle reduce the resistance of the independent performance of hemoglobin levels.

The human data on the relationship of deposits of iron and aerobic capacity are more complex to interpret, as the decrease of hemoglobin figures confuses the expression of the direct effects of iron deficiency in the skeletal muscle. However, small controlled clinical studies have shown that iron deficiency, more than the concentration of hemoglobin, is associated with deterioration of physical resistance in the exercise to the highest levels in subjects with HF[47]. Furthermore, in a European study of cohort with 1278 patients with HF sampled, the combined influence of iron deficiency and anemia was explored by different regression multivariable models, demonstrating the negative impact of iron deficiency on the quality of life, independent of the presence of anemia[48].

Taken these results together with those ones obtained in animals --, support the hypothesis that the improvement in the functional capacity, after the supplementation of iron per track IV in non anemic patients with HF, can be partially attributable to the increase in the oxidative capacity associated with deposits replete of iron that that contain oxidative enzymes.

Comments and Conclusions

Although the current European guidelines on the management of the HF recognize that iron deficiency is a common comorbidity and clinically relevant, the recommendations for its treatment are weak, due to lack of evidence. On the other hand, IV therapy with iron is not included within the standard guidelines for the management of the HF, because the improvement in the PC6M is insufficient to establish a recommendation class I for all patients with HF and, in addition, the potential benefits on morbidity and mortality are not checked. While the improvement consisting in the results of the PC6M and in the functional class and the reduction of the risk of hospitalization due to worsening of the HF are important variables, represent indirect evidence of the effect of iron, but lack information on the heart function.

Accordingly, despite the fact that the data from the studies are promising, it requires a controlled clinical trial (RCT by randomized controlled trial), with the largest number of participants and the duration of the observation, especially focused on the iron preparations with their doses, different levels of hemoglobin and cardiac function (ejection fraction, mainly), to establish the HF as an indication of the parenteral treatment with iron.

However, based on the studies reviewed here, IV therapy with iron should be taken into account in patients with iron deficiency and persistence of symptoms and deterioration in the quality of life, in spite of receiving the therapies classified as Class I and considering the values of ferritin and transferrin saturation[49,50].

The administration of iron by mouth in patients with HF is not recommended for the following reasons[51,52]:

- Lack of controlled studies demonstrating their effectiveness.
- Gastrointestinal effects frequent adverse

- To perceive increase in the hemoglobin, long time of administration is required.

An important aspect to highlight is that irrespective of the formulation of parenteral iron used, there always remains small quantities of labile iron circulating freely in plasma that can induce adverse reactions (redness, vasodilation, myalgia, edema of limbs and, rarely, nausea) on sensitive subjects. The effects are usually mild, limited and transitory that usually do not require treatment[53].

Conflict of Interest

The authors state that they do not have a conflict of interest.

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