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PREVALENCE OF ANEMIA IN PATIENTS WITH CONGESTIVE HEART FAILURE A PROSPECTIVE STUDY

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Abstract

Anemia is known to be associated with heart failure (HF), but it is not widely considered in patients with HF. The aim of this study is to assess the prevalence of anemia among CHF patients and to evaluate its treatment in patient with CHF. Methods. Participants were enrolled by a process of simple random sampling of patients. Serum ferritin was measured using a fully automated bidirectional interfaced chemi-doppler echocardiography. Results. There was a significant increase in the number of patients with CRD, including its most severe forms, and the increasing predominance of vascular diseases within the CRD. The study also expects to evaluate the common type of anemia and to have a positive impact significant and knowledge on anemia and its treatment. Conclusions This study showed that there is a large burden of iron deficiency and anemia in patients of CHF, though other causes need to be excluded.

Keywords: *Anemia, Heart Failure, CHF, Chemi-Doppler.*

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1. Introduction

Anaemia is defined by WHO as Hb < 13.0 g/dL in male adults and <12.0 g/dL in female adults.1 It is one of the commonest associations in patients of HF2,3 and has been shown to be as- sociated with increased mortality in both acute and chronic heart failure.4,5 The aetiology is varied, especially in countries like India where apart from other mechanisms, nutritional de- ficiency and worm infestations also play a part. ID has emerged as one of the most important causes of anaemia in patients of heart failure, though other causes need to be excluded as well. Iron is an essential element for humans due to its role in several functions in our bodies. There are several physiological conditions where its deficiency occurs. These are infancy, pregnancy, lactation, menstrual periods, and old age. As a majority of patients of HF are in the elderly age group, it is also important to exclude other causes of anaemia such as GI malignancies which have been reported to be present in about 10% of patients undergoing endo- scopic evaluation in a large study.6 Over the past few years, a lot of research has been carried out into ID in conditions such as chronic kidney disease, HF, chronic inflammatory dis- eases, and cancer, and several mechanisms have been eluci- dated and corrective steps identified.

Types

There are many forms of anemia, and each type has telltale symptoms. Some common types of anemia include:

- iron deficiency anemia
- vitamin B12 deficiency anemia
- aplastic anemia
- hemolytic anemia
- microcytic,
- normocytic or macrocytic

Anemia with Congestive Heart Failure

Anemia is known to be associated with heart failure (HF), but it is not widely considered in clinical practice. Previous works[1] that pointed out the role of anemia as a risk factor in this complex condition were not received with much acceptance. This situation has recently taken a notable turn and anemia has come to occupy a more relevant position in the understanding of the pathogenesis of heart failure. In an illustrative example, while the clinical guidelines for the management of HF issued by the American College of Cardiology and the American Heart Association between 1999 and 2001[2] did not mention anemia, in those of 2005,[3] it is recognized as a frequent finding that is associated with the rates of morbidity and mortality. From that time on, the data has become increasingly extensive, and a recent review of new aspects of HF[4] acknowledges an even more relevant pathogenic role of anemia than that mentioned in the European guidelines for HF.[5] This recognition has generated a high level of expectation with respect to the possible beneficial role of the treatment of anemia in the natural history of HF. This expectation, however, has not been accompanied by the systematization of its study and treatment. In contrast, there has been a progressive increase in the application of therapeutic measures, not always sufficiently individualized and systematized. All in all, anemia in patients with heart failure is still enveloped in unknowns, especially with respect to its pathogenesis and the importance of its course in HF, constituting a terrain in which opinion still predominates over scientific evidence.

Prevalence of Anaemia in HF

Anaemia is highly prevalent in patients of heart failure. In the first multi-ethnic Asian-HF study, it was present in one third.

2. Epidemiology and Magnitude of the Problem

The Prevalence Depends on the Population Being Studied and the Comorbidity

In published series, the percentage of patients in which HF is accompanied by anemia differs widely,[6,7] ranging between 9.9%[8] and over 50%.[9] This variability depends in part on the differences between the populations analyzed (comorbidity, New York Heart Association [NYHA] class), but, above all, on the cutoff point used to define anemia.

Patients with anemia and HF tend to be of more advanced age, in NYHA functional class III-IV, with more drug treatment and more comorbidity (diabetes mellitus, chronic renal disease [CRD], and hypertension), as well as longer and more frequent hospital stays,[6,10] but these individuals are not

usually included in drug trials.[11] As an example, in an analysis of older patients, more than half had a hemoglobin level < 12 g/dL and, among this subgroup, 79.1% were in NYHA class IV.[12] A large body of data supports the concept that the prevalence of anemia increases with more severe HF, but they do not explain the mechanisms involved in this relationship.

The Estimation of the Prevalence Depends on the Definition of Anemia

A major drawback when assessing population-based data is the fact that uniform cutoff points have not been employed to define anemia. At the present time, the situation remains unstable in terms of definition. The clearest example is that observed in renal patients. In individuals with CRD, the National Kidney Foundation (NKF), in its 2000 guidelines, defined anemia as a hemoglobin level < 12.0 g/dL in men and postmenopausal women.[14] In a new version of these guidelines (2006), the limits were raised to < 13.5 g/dL in men and remained at < 12 g/dL in women.[15] However, the publication of new works in the months following the appearance of these modified guidelines (see section on "Current perspectives") has led to their immediate revision, and a third version is now being drafted in which lower target hemoglobin values are again being proposed (Adeer Levin, personal communication, 2007). As a whole, the instability of this issue is a clear invitation to act with caution when establishing objectives in the anemia of HF.

According to a review on the prevalence of anemia in HF,[6] the most widely used cutoff point is hemoglobin < 12 g/dL. This is not a trivial detail since a change in the cutoff point of 1 g/dL for hemoglobin or of 1% for hematocrit produces a substantial change in the prevalence.[9] For example, in the Euro-Heart Failure Study,[16] the estimate of the prevalence of anemia increased by 33% with the cutoff point of 12 g/dL. Finally, the World Health Organization utilizes limits of hemoglobin < 12 g/dL in regularly menstruating women and < 13 g/dL in men and in postmenopausal women.

Along these lines of interpretation, a central idea is that, in the context of cardiovascular disease, asymptomatic anemia does not exist. That means that the classification of an individual as anemic and, thus, in need of treatment takes on unforeseen implications in terms of the possible administration of costly drug treatments.

3. Pathophysiology and Pathogenesis

Heart failure, like other chronic diseases, is practically nonexistent outside the human species. The adaptive mechanisms are changes in physiological responses, originally developed for other purposes. In nature, anemia depends nearly exclusively on hemorrhage, and induces the activation of mechanisms to maintain perfusion, and the oxygen supply to tissues, but also to preserve volume. Focusing on the hemorrhage, the organism sets in motion an integrated response with actions in different regions, which include vasoconstriction and thrombosis, fluid retention, stimulation of erythropoiesis, and vascular repair. It is interesting to observe that the system most competent in inducing sustained vasoconstriction, the renin-angiotensin-aldosterone system (RAAS), is also pivotal in a mechanism capable of activating many of the aforementioned functions, including vascular fibrous scar formation.

In the presence of anemia, the heart undergoes remodeling, and both the sympathetic nervous system and the RAAS contribute to this phenomenon. In this respect, taking into account the recently discovered trophic role of EPO in the prevention of cardiomyocyte apoptosis,21 as well as in myocardial revascularization, an EPO deficiency can result in important defects in remodeling. In other words, EPO may be necessary, or at least useful, in the maintenance of myocardial viability in the presence of anemia and under other circumstances. Myocardial failure itself, through the secretion of cytokines such as tumor necrosis factor alpha (TNF-α), can, in turn, worsen anemia, completing the vicious circle, with extremely negative results.22 However, if we review the available scientific evidence, we discover that there is a lack of validated data, obtained with current techniques, concerning critical aspects of the sequence of events leading to anemia. Moreover, a considerable portion of the concepts employed is based on extrapolations of findings in normal physiology, or even intuitive ideas. An important reason for this lack is the result of the absence of studies on this subject in experimental models of HF.

4. Pathogenic Factors Related to Anemia in Heart Failure

Of the few attempts to establish the pathogenic classification of anemia in HF, most have corresponded to the pattern described for anemia associated with chronic diseases[23] (58%) and, less frequently, to iron deficiency (21%), nutritional deficiencies (8%), and other causes, including chronic bleeding in patients receiving antiplatelet or anticoagulant therapy (13).[10] However, in recent series, on paper, a more important role is granted to iron deficiency, which is reported to be a major cause of anemia in nearly 80% of the cases.[24] In any case, it can be considered to be multifactorial and always requires a highly individualized study and treatment.

Chronic Renal Disease and Cardio Renal Failure

Two aspects of the new epidemiology of CRD have direct consequences in patients with HF: the marked increase in the number of patients with CRD, including its most severe forms, and the significant change in the causes, with a growing predominance of vascular diseases, within the arteriosclerosis-hypertension-diabetes complex.[25,26] Of maximum interest, the conditions that lead to renal failure in these individuals basically overlap those that favor HF and ischemic heart disease; thus, we observe a situation in which the 3 diseases, CRD, HF, and ischemic heart disease, can coincide.

5. Aim and Objective

Aim

The study aims to carry out the prevalence of anemia among CHF in patient.

Primary Objective

To evaluate the laboratory parameters associated with anemia in Heart Failure patients and to assess its prevalence.

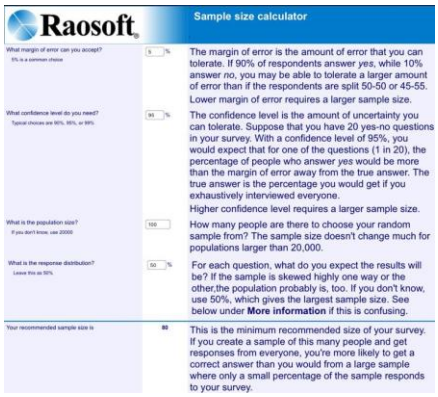
Second Objective

To identify the type of anemia the most commonly prevention and control among CHF in the respective population and to impact knowledge among patients regarding the significance of anemia in CHF

Material and Methods

Methodology

Sample Size



$$x = Z(^{c}/_{100})^{2}r(100-r)$$
$$n = {}^{N\,x}/_{((N-1)E^{2}\,+\,x)}$$
$$E = \mathrm{Sqrt}[{}^{(N\,-\,n)x}/_{n(N-1)}]$$

Study Design

Prospective Study.

Study Duration

6 months.

Complete Study Procedure

Participants for this study were enrolled by a process of simple random sampling of patients attending the out-patient clinic of the Department of Cardiology, St. Isabel's Hospital, who met the pre-specified inclusion and exclusion criteria. Controls were chosen from apparently healthy family members of patients admitted in the Institute of Internal Medicine, St. Isabel's Hospital, after ensuring that they too met the pre-specified inclusion and exclusion criteria. Age-matched controls were chosen, such that number of cases and number of controls below the age of 60 were equal. Similarly, there were an equal number of cases and controls who were aged over 60 years. Informed consent was obtained from all participants. They were subjected to thorough history-taking and clinical examination.

Fresh peripheral venous blood samples were collected in ethylene diaminetetraacetic acid (EDTA) and serum tubes and sent for analysis. A complete haemogram with red cell indices was performed. Serum ferritin was measured using a fully automated bidirectionally interfaced chemi luminescent immuno assay.

Serum iron was measured by the ferrozine method without deproteinisation. Total iron binding capacity (TIBC) was measured by a spectrophotometric assay. Transferrin saturation was calculated as 100 x serum iron / TIBC.

Participants were subjected to a comprehensive transthoracic Doppler echocardiography, performed using standardised equipment. The biplane method of disks was used to evaluate left ventricular ejection fraction.

Inclusion Criteria for Cases

1. Patients with typical symptoms and signs of heart failure (OR) Asymptomatic patients who are on anti-failure pharmacotherapy for a previous episode of symptomatic heart failure.
2. Ejection fraction <40% years.
3. Age >40 years.

Exclusion Criteria for Cases

1. Patients with specific aetiologies for heart failure (eg, valvular heart disease, congenital heart disease).
2. Hospitalisation, acute coronary syndrome or coronary revascularization over the last 30 days.
3. Any acute/chronic illness other than heart failure that may influence iron metabolism (including known malignancy, active bleeding, infection, severe renal disease requiring dialysis, haematological diseases).
4. Treatment for anaemia and/or iron deficiency (blood transfusions, erythropoietin therapy, iron supplements) within the last 6 months.

Effect of Sex on Iron Deficiency

Table 1: Effect of Sex on Iron Deficiency

Sex	Iron-deficient cases	Iron-deficient controls	Total
Male	19	8	27
Female	17	10	27
Total	36	18	54

- Percentage of cases with iron deficiency who are male=52.8%
- Percentage of cases with iron deficiency who are female=47.2%
- Percentage of controls with iron deficiency who are male=44.4%
- Percentage of controls with iron deficiency

who are female=55.6%

- The Null Hypothesis in this case is "There is no significant effect of sex on the prevalence of iron deficiency, among cases and controls"
- Degree of freedom=1
- Chi-square statistic=0.333
- P-value=0.5638
- Thus, the Null Hypothesis is true.

Distribution of Iron Deficiency by NYHA Classification

Table 2: Distribution of Iron Deficiency by NYHA Classification

NYHA classification	Iron deficiency present	Iron deficiency absent	Total
Class1	3	5	8
Class2	17	7	24
Class3	9	1	10
Class4	7	1	8
Total	36	14	50

- Percentage of iron deficiency in NYHAClass1=37.5%
- Percentage of iron deficiency in NYHAClass2=70.8%
- Percentage of iron deficiency in NYHAClass3=90%
- Percentage of iron deficiency in NYHAClass4=87.5%
- The Null Hypothesis in this case is "There is no significant effect of NYHA class on the presence or absence iron deficiency"
- Degree of freedom=3
- Chi-square statistic=7.3
- P-value=0.06
- Thus, the Null Hypothesis is true.

Effect of Age on Anaemia

Table 3: Effect to Fageon Anaemia

Age	Cases with Anaemia	Controls with Anaemia	Total
Age<60years	7	8	15
Age>60years	20	6	26
Total	27	14	41

- Percentage of cases with anaemia aged<60years=25.9%
- Percentage of cases with anaemia aged>60years=74.1%
- Percentage of controls with anaemia aged<60years=57.1%
- Percentage of controls with anaemia aged>60years=42.9%
- The Null Hypothesis in this case is "There is no significant effect of age on the prevalence of anaemia, among cases and controls"
- Degree of freedom=1
- Chi-square statistic =3.873
- P-value=0.049
- Thus, the Null Hypothesis is rejected.

Effect of Sex on Anaemia

Table 4: Effect of Sex on Anaemia

Sex	Cases with anaemia	Controls with anaemia	Total
Male	11	4	15
Female	16	10	26
Total	27	14	41

- Percentage of cases with anaemia who are male=40.7%
- Percentage of cases with anaemia who are female=59.3%
- Percentage of controls with anaemia who are male=28.6%
- Percentage of controls with anaemia who are female=71.4%
- The Null Hypothesis in this case is "There is no significant effect of sex on the prevalence of anaemia, among cases and controls"
- Degree of freedom=1
- Chi-square statistic=0.588
- P-value=0.443
- Thus, the Null Hypothesis is true.

Anemia in Cases and Controls

Table 5: Anemia in Cases and Controls

	Cases	Controls	Total
Anemia present	27	14	41
Anemia absent	23	36	59
Total	50	50	100

- Prevalence of anemia in subjects in cases (with heart failure) =54%
- Prevalence of anemia in subjects in controls (without heart failure) =28%
- Odds ratio=3.01
- The Null Hypothesis in this case is "There is no significant difference in the prevalence of anemia, between cases and controls"
- Degree of freedom=1
- Chi-square statistic=6.986
- P-value= 0.008
- Thus, the Null Hypothesis is rejected.

Frequency of Anemia in Patients who are Iron Deficient

Table 6: Frequency of Anemia in Patients who are Iron Deficient

	Cases who are iron deficient	Controls who are iron deficient	Total
Anemia present	26	14	40
Anemia absent	10	4	14
Total	36	18	54

- Prevalence of anemia in cases who are iron deficient=72.2%
- Prevalence of an anemia in controls who are iron deficient=77.7%
- The Null Hypothesis in this case is "There is no significant effect of the presence or absence of anemia on the prevalence of iron deficiency among cases and controls"
- Degree of freedom=1
- Chi-square statistic=0.193
- P-value=0.6604
- Thus, the Null Hypothesis is true.

Effect of Antiplatelets on Iron Deficiency Among Cases

Table 7: Effect of Antiplatelets on Iron Deficiency Among Cases

	Iron deficiency present	Iron deficiency absent	Total
Taking antiplatelet agents	25	9	34
Not taking antiplatelet agents	11	5	16
Total	36	14	50

- Prevalence of iron deficiency in patients taking antiplatelets =73.5%
- Prevalence of iron deficiency in patients not taking antiplatelets=68.75%
- TheNullHypothesis in this case is "The use of antiplatelet agents has no significant effect on the presence or absence of irondeficiency"
- Degree of freedom=1
- Chi-square=0.123
- P-value=0.7258
- Thus, the Null Hypothesis is true

6. Discussion

For this study, 50 patients with heart failure with reduced ejection fraction (HFrEF; left ventricular ejection fraction <40%) who met the pre-specified inclusion and exclusion criteria were chosen. For comparison, 50 controls were chosen who were age-matched to the cases, and had no clinical or echocardiography evidence of heart failure, which met the pre-specified inclusion and exclusion criteria, were also included in the study. A detailed history was taken and clinical examination was performed. Peripheral venous blood was drawn, and a complete hierogram along with iron studies (iron, ferrit in, transfer in saturation and total iron binding capacity) were performed.

7. Conclusion

This study showed that there is a large burden of iron deficiency and anemia in patients with heart failure with reduced ejection fraction, with iron deficiency being more common. It has been proved in randomized-controlled trials that correction of this iron deficiency, irrespective of the presence or absence of concomitant anemia, improves quality of life. It may therefore be prudent to assess and use iron status as a therapeutic target in all patients with heart failure. This is especially true of a country like India where a significant proportion of the population is iron deficient.

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