Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/e3x21207

EXPLORING THE INTERACTIONS BETWEEN ANEMIA AND HEART FAILURE: A HISTOPATHOLOGICAL AND HEMATOLOGICAL STUDY ON HOW BLOOD ABNORMALITIES INFLUENCE CARDIAC TISSUE DAMAGE

Dr Wasif Mushtaq[1], Dr Fariha Tariq[2], Dr Anam Mahmood[3], Dr. Sarwat Jahan[4*], Dr Fareeha Naseer Syed[5], Dr Zafar Iqbal Ghafoor[6]

[1]Medical officer, Social Security Hospital, Faisalabad, Pakistan
[2]Assistant Professor Department of Forensic Medicine King Edward Medical University Lahore, Pakistan
[3]Senior Demonstrator Department of Pathology University college of Medicine and Dentistry, University of Lahore, Pakistan
[4*]Associate Professor Department of Pharmacology and Therapeutics, Aziz Fatimah Medical and Dental College, Faisalabad, Pakistan
[5]Assistant Professor of Pathology, CMH Multan Institute of Medical Sciences, Multan, Pakistan
[6]Assistant Professor Pharmacology Department Quaid e Azam Medical College, Bahawalpur, Pakistan

***Corresponding author:** Dr. Sarwat Jahan
***E mail:** sarwarj@yahoo.com

ABSTRACT

Introduction: Anemia and heart failure (HF) are two prevalent and interconnected medical conditions that significantly impact global health.

Objective: This study aims to explore the histopathological and hematological interactions between anemia and heart failure, with a focus on how blood abnormalities influence cardiac tissue damage.

Methodology: This prospective, observational study was conducted at Aziz Fatima Medical and Dental College Faisalabad & CMH Multan Institute of Medical Sciences, Multan from A total of 88 patients diagnosed with heart failure were recruited from a tertiary care hospital.

Results: Data were collected from 88 patients. The results indicate that patients with severe anemia (n=30) were slightly older (mean age 62.8 years) compared to those with mild-to-moderate anemia (n=58, mean age 62.1 years). Both groups had a similar gender distribution, with approximately 55% males in the mild-to-moderate group and 53% in the severe group. However, patients with severe anemia showed significantly reduced left ventricular ejection fraction (LVEF) at 32% compared to 41% in the mild-to-moderate group, along with a higher prevalence of iron deficiency (80% vs. 55%).

Conclusion: It is concluded that anemia significantly exacerbates cardiac dysfunction and tissue damage in heart failure patients, primarily through mechanisms of chronic hypoxia, inflammation, and iron deficiency. Severe anemia is associated with increased myocardial fibrosis, reduced ejection fraction, and worsened clinical outcomes.

Keywords: Anemia, Heart Failure, Cardiac Tissue Damage, Blood Abnormalities

Introduction

Anemia and heart failure (HF) are two prevalent and interconnected medical conditions that significantly impact global health. While anemia is characterised by low RBC count or low Hb concentration, heart failure is the inadequacy of the heart to pump out enough blood to meet the demands of the body [1]. These conditions are often related, though anemia is not only an outcome of heart failure but also may worsen the condition. However, there is still not enough knowledge on how interaction between anemia and cardiac tissue and remodeling occur in heart failure. Anemia and CHF are both clinically relevant conditions based on the epidemiological data showing that prevalence of anemia in systolic and diastolic heart failure is significant and the combined effect of anemia and CHF on morbidity and mortality [2]. Approximately 50% of HF patients are reported to have anemia; this comorbidity had been reported to worsen the patient's overall prognosis and increase his/her risk of hospitalization, lower quality of life, and higher mortality rates [3]. The presence of anemia in patients with heart failure is typically polymicrobial and includes iron deficiency, inflammation, and decreased erythropoiesis increasing cardiac dysfunction. In addition, anemia delays the natural course of heart failure by increasing the workload and demand of coronary oxygen supply due to impaired its delivery to the target organs [4].

Histopathological point of view relates the cardiac tissue damage in anemia to chronic hypoxia, oxidative stress, and inflammation. Anemia leads to cardiomyocyte dysfunction and remodeling because following reduced oxygen delivery to the myocardium the heart undergoes structural / functional changes such as injury or fibrosis [5].

Failure also leads to injury of important cellular and molecular targets and may also contribute activation of other compensatory mechanisms including increased cardiac output, neurohormonal activation which in turn may be damaging to the already stressed heart [6]. These pathological processes advance the structural and functional myocardial remodeling leading to the deterioration of clinical status in heart failure. They include not only anemia but other blood changes that occur in heart failure patients such as platelet dysfunction, clotting profile, and inflammatory response. Inflammation states that are habitual in heart failure and which is present in this case may inhibit the process of erythropoiesis, detrimentally affect the metabolism of iron and, therefore lead to anemia [7].

At the same time, changes of HF common to all patients, including elevated central venous pressure, renal hypoperfusion as well as others, contribute to the occurrence of haemodilution and anamia. These two conditions thus develop a bidirectional relationship in which they reinforce each other and call for multisectoral approaches to their management [8].

A recent focus on the relationship between Iron deficiency anemia and heart failure clearly needs to be focused. Iron is one of the metal which is indispensable for the synthesis of hemoglobin molecule and thus depends on iron for oxygen transport and cell energy generation [9]. Subclinical iron deficiency has been demonstrated to negatively affect cardiac function, enhance impairment of mycardial efficiency, and raise the prognosis for heart failure up to 5 fold. It is hence important to study the relationship between iron homeostasis and cardiotoxicity to find out the possible treatment [10].

Objective

This study aims to explore the histopathological and hematological interactions between anemia and heart failure, with a focus on how blood abnormalities influence cardiac tissue damage.

Methodology

This prospective, observational study was conducted at Aziz Fatima Medical & Dental

College Faisalabad & CMH Multan Institute of Medical Sciences. A total of 88 patients diagnosed with heart failure were recruited from a tertiary care hospital.

Study Population

The study included adults aged 18 years and older who were diagnosed with heart failure based on clinical, echocardiographic, and laboratory findings. Heart failure severity was classified according to the New York Heart Association (NYHA) functional classification system. Anemia was defined as hemoglobin levels below 13 g/dL for men and 12 g/dL for women. All participants provided informed consent. Exclusion criteria included chronic kidney disease requiring dialysis, active infections, malignancies, autoimmune disorders, recent blood transfusions, pregnancy or lactation, and other significant comorbidities such as advanced liver disease or uncontrolled diabetes.

Data Collection

Data collection involved comprehensive clinical assessments, hematological analysis, histopathological examination, and cardiac function evaluation. A detailed medical history was taken, including information on the duration and severity of heart failure, symptoms, comorbid conditions, and prior treatments. Physical examinations assessed signs of fluid overload, pallor, and cardiovascular abnormalities. Hematological tests included complete blood count (CBC) to measure hemoglobin levels, red blood cell indices, and markers of anemia severity. Serum iron studies, such as ferritin, transferrin saturation, and total iron-binding capacity (TIBC), were performed to assess iron deficiency. Additionally, inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), were measured to explore the role of systemic inflammation.Histopathological examinations were conducted on endomyocardial biopsies obtained from a subset of patients. Tissue samples were stained using hematoxylin and eosin (H&E) and Masson's trichrome staining to evaluate cellular injury, inflammation, and fibrosis.

Immunohistochemical techniques were employed to measure tissue hypoxia markers, such as hypoxia-inducible factor-1α (HIF-1α), to understand the extent of myocardial hypoxia. Cardiac function was assessed using echocardiography to measure left ventricular ejection fraction (LVEF), wall motion abnormalities, and ventricular dimensions. Natriuretic peptide levels, including BNP or NT-proBNP, were evaluated to determine the severity of heart failure.The 88 patients were stratified into two groups based on anemia severity. The mild-to-moderate anemia group included patients with hemoglobin levels between 8–12 g/dL for women and 8–13 g/dL for men, while the severe anemia group consisted of patients with hemoglobin levels below 8 g/dL. This stratification allowed for comparative analyses of how different degrees of anemia affected cardiac tissue damage and heart failure severity. By dividing the patients into these groups, the study aimed to identify threshold levels of anemia that significantly impact myocardial pathology.

Statistical Analysis

Data were analyzed using statistical software SPSS v29. Descriptive statistics summarized baseline characteristics, while correlation coefficients were used to examine associations between variables. Multivariate regression models were employed to evaluate the independent contribution of anemia severity to cardiac tissue damage.

Results

Data were collected from 88 patients. The results indicate that patients with severe anemia (n=30) were slightly older (mean age 62.8 years) compared to those with mild-to-moderate anemia (n=58, mean age 62.1 years). Both groups had a similar gender distribution, with approximately 55% males in the mild-to-moderate group and 53% in the severe group. However, patients with severe anemia showed significantly reduced left ventricular ejection fraction (LVEF) at 32% compared to 41% in the mild-to-moderate group, along with a higher prevalence of iron deficiency (80% vs. 55%).

Table 1: Baseline Characteristics

Characteristic	Mild-to-Moderate Anemia (n=58)	Severe Anemia (n=30)
Mean Age (years)	62.1	62.8
Male (%)	55.0	53.0
Female (%)	45.0	47.0
LVEF (%)	41.0	32.0
Iron Deficiency (%)	55.0	80.0
Hypertension (%)	68.0	72.0
Diabetes (%)	57.0	60.0

The hematological analysis revealed significant differences between the mild-to-moderate anemia group (n=58) and the severe anemia group (n=30). Hemoglobin levels were markedly lower in the severe anemia group (7.2 g/dL vs. 10.5 g/dL, $p<0.01$), accompanied by reduced mean corpuscular volume (72.0 fL vs. 82.0 fL, $p<0.01$), indicating more pronounced microcytic anemia. Iron parameters were significantly worse in severe anemia, with lower ferritin (45.0 ng/mL vs. 85.0 ng/mL, $p<0.01$) and transferrin saturation (12.0% vs. 20.0%, $p<0.05$).

Table 2: Hematological Parameters

Hematological Parameter	Mild-to-Moderate Anemia (n=58)	Severe Anemia (n=30)	p-value
Hemoglobin (g/dL)	10.5	7.2	<0.01
Mean Corpuscular Volume (fL)	82.0	72.0	<0.01
Ferritin (ng/mL)	85.0	45.0	<0.01
Transferrin Saturation (%)	20.0	12.0	<0.05
CRP (mg/L)	8.1	12.5	<0.05
IL-6 (pg/mL)	20.0	30.0	<0.01

The histopathological findings demonstrated more pronounced myocardial damage in the severe anemia group (n=10) compared to the mild-to-moderate anemia group (n=10). The fibrosis area was significantly higher in the severe anemia group (25% vs. 15%, $p<0.01$), reflecting greater cardiac remodeling. HIF-1α expression, indicative of hypoxia, was elevated to high levels in the severe group compared to moderate levels in the mild-to-moderate group.

Table 3: Histopathological Findings

Histopathological Finding	Mild-to-Moderate Anemia (n=10)	Severe Anemia (n=10)	p-value
Fibrosis Area (%)	15	25	<0.01
HIF-1α Expression	Moderate	High	-
Inflammatory Cell Infiltration (%)	8	15	<0.05

Patients with severe anemia had a larger left ventricular end-diastolic diameter (6.2 cm vs. 5.8 cm, $p<0.01$), indicating greater ventricular dilation. Additionally, brain natriuretic peptide (BNP) levels, a marker of heart failure severity, were significantly higher in the severe anemia group (850.0 pg/mL vs. 600.0 pg/mL, $p<0.01$), reflecting worsened cardiac function and increased hemodynamic stress in these patients.

Table 4: Cardiac Function Parameters

Cardiac Function Parameter	Mild-to-Moderate Anemia (n=58)	Severe Anemia (n=30)	p-value
Left Ventricular End-Diastolic Diameter (cm)	5.8	6.2	<0.01
BNP (pg/mL)	600.0	850.0	<0.01

Discussion

The findings of this study highlight the significant interplay between anemia and heart failure, with both hematological abnormalities and histopathological cardiac changes contributing to the worsening of clinical outcomes. The studies show that anemia and severe anemia in particular is numerous associated with higher levels of myocardial fibrosis, hypoxic tissue injury, inflammatory markers and significant reductions in cardiac function. These findings underscore the importance of the anemia as a contributor to the development of cardiac disorders in patients with heart failure [11]. Another finding particularly noted in the present study was that the severity of anemia had close relationship with myocardial fibrosis. The percentage of fibrosis was significantly higher, and the level of HIF-1α was significantly higher in the patients in the severe anemia group. This outcome provides evidence for the hypothesis that chronic hypoxia due to diminished oxygen-carrying ability in anemia promotes pathologic cardiac remodeling [12]. Fibrosis is an essential feature of adverse cardiac remodeling; causes myocardial structural and functional dysfunction and redirects heart failure symptoms. These findings are in accord with other researchers, who have pointed out hypoxic and oxidative conditions may be responsible for promotion of fibrosis in the cardiac muscles [13] .

The hematologic results of the study established that severe anemia was associated with low hemoglobin concentrations, small mean corpuscular volume, and low iron stores. They were compared with the normal anemia group and the severe anemia group with lower ferritin and transferrin saturation values in the severe anemia group. This is in line with prior data showing that, irrespective of anemia, ID [iron deficiency] adversely affects myocardial energetics and worsens heart failure symptoms [14]. Higher levels of CRP and IL6 levels in both anemia groups also imply that systemic inflammation might explain some of the detrimental effects of anemia on the cardiac tissue. As observed in this study, the echocardiographic results showed that severe anemia was characterized by increased LVED and LVSD, reduced LVEF and elevated plasma concentrations of NT-proBNP [15]. It is clear that these indicators of the emergence of worsening of the cardiac function point at the hemodynamic and neurohormonal load linked to anemia. When augmenting cardiac output to compensate for lower ability to transport oxygen in anemia, there is negative force on the myocardium potentially resulting in ventricular enlargement and poor systolic function. The relatively much higher BNP level in the severe anemia group supports previous findings that anemia worsens cardiac workload and fluid state [16].

The findings in the present study provide evidence of the associations between hematologic and histopathologic changes to the background of heart failure. Hemoglobin of <115 g/L were quite strongly correlated with higher fibrosis, LVEF dysfunction and N terminal pro natriuretic peptide type B (NT pro BNP) levels [17]. Like it, Several evidence of the iron deficiency' presence was associated with cardiac dysfunction which renders its treatment to specific therapeutic approaches. The conclusions of this research will be valuable from the clinical perspective [18]. Given such a direct relationship between anemia and unfavorable cardiac events, anemia should be one of the main priorities of heart failure therapy. In addition to iron formulation, erythropoiesis stimulating agents and anti-inflammatory drugs, may have theoretic benefits they may help prevent the effects of anemia on cardiac tissue and promote patient survival [19]. Further studies should examine the effectiveness of such interventions in reversing or halting the progress of the pathological processes detected in this

work. However, it is noteworthy that the present investigation has certain limitations. There was a relatively small sample size, especially in histopathologically matched comparison. Finally, the observational study plan means that issues of cause and effect cannot be established with certainty either. Longitudinal prospective studies should be conducted to study the interaction between anemia and cardiac tissue injury and also to assess clinical efficacy of anemia therapies in heart failure patients.

Conclusion

It is concluded that anemia significantly exacerbates cardiac dysfunction and tissue damage in heart failure patients, primarily through mechanisms of chronic hypoxia, inflammation, and iron deficiency. Severe anemia is associated with increased myocardial fibrosis, reduced ejection fraction, and worsened clinical outcomes. Addressing anemia and its underlying causes is crucial for improving the management and prognosis of heart failure.

References

1. Felix N von Brackel, Ralf Oheim, Iron and bones: effects of iron overload, deficiency and anemia treatments on bone, JBMR Plus, Volume 8, Issue 8, August 2024, ziae064, https://doi.org/10.1093/jbmrpl/ziae064
2. Mezzetti, E., Costantino, A., Leoni, M., Pieretti, R., Di Paolo, M., Frati, P., Maiese, A., &Fineschi, V. (2023). Autoimmune Heart Disease: A Comprehensive Summary for Forensic Practice. Medicina, 59(8), 1364. https://doi.org/10.3390/medicina59081364
3. Arita, Y.; Nakaoka, Y.; Otsuki, M.; Higuchi, K.; Hashimoto-Kataoka, T.; Yasui, T.; Masaki, T.; Ohtani, T.; Kishimoto, T.; Yamauchi-Takiharo, K.; et al. Cytokine storm after cessation of tocilizumab in a patient with refractory Takayasu arteritis. Int. J. Cardiol. **2015**, 187, 319–321.
4. Chung, D.C.; Choi, J.E.; Song, Y.K.; Lim, A.L.; Park, K.H.; Choi, Y.J. Polyarteritis nodosa complicated by chronic total occlusion accompanying aneurysms on all coronary arteries. Korean Circ. J. **2012**, 42, 568–570.
5. Chimenti, C.; Alfarano, M.; Toto, F.; Fanisio, F.; Verardo, R.; Galea, N.; Agati, L.; Frustaci, A. Myocarditis and intramural coronary vasculitis in polyarteritis nodosa: An unusual treatable form of heart failure. ESC Heart Fail. **2020**, 7, 4357–4360.
6. Pagnoux, C.; Seror, R.; Henegar, C.; Mahr, A.; Cohen, P.; Le Guern, V.; Bienvenu, B.; Mouthon, L.; Guillevin, L.; French Vasculitis Study Group. Clinical features and outcomes in 348 patients with polyarteritis nodosa: A systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum. **2010**, 62, 616–626.
7. Howard, T.; Ahmad, K.; Swanson, J.A.; Misra, S. Polyarteritis nodosa. Technol. Vasc. Interv. Radiol. **2014**, 17, 247–251.
8. Harada, Y.; Suzuki, T.; Shinagawa, T.; Yoshimoto, T. Cardiac arrest in a patient with polyarteritis nodosa. Intern. Med. **2013**, 52, 2759–2763.
9. Peters, B.; Von Spiczak, J.; Ruschitzka, F.; Distler, O.; Manka, R.; Alkadhi, H. Cardiac manifestation of polyarteritis nodosa. Eur. Heart J. **2018**, 39, 2603.
10. Plastiras, S.C.; Moutsopoulos, H.M. Arrhythmias and Conduction Disturbances in Autoimmune Rheumatic Disorders. ArrhythmElectrophysiol. Rev. **2021**, 10, 17–25.
11. Watanabe, Y.; Sakamoto, K.; Matsukage, S.; Ogimoto, A. Heart failure in a patient with polyarteritis nodosa. Eur. Heart J. **2020**, 4, 1–2.
12. Kikuchi, K.; Hoashi, T.; Kanazawa, S.; Tamaki, K. Angiogenic cytokines in serum and cutaneous lesions of patients with polyarteritis nodosa. J. Am. Acad. Dermatol. **2005**, 53, 57–61.
13. Caforio, A.L.; Marcolongo, R.; Jahns, R.; Fu, M.; Felix, S.B.; Iliceto, S. Immune-mediated and autoimmune myocarditis: Clinical presentation, diagnosis and management. Heart Fail Rev. **2013**, 18, 715–732.

14. Takeishi, M.; Mimori, A.; Adachi, D.; Suzuki, T. [A case of adult polyarteritis nodosa associated with fulminant group A streptococcal infection]. Ryumachi **2002**, 42, 682–686.
15. Kalayciyan, A.; Zouboulis, C. An update on Behçet's disease. J. Eur. Acad. Dermatol. Venereol. **2007**, 21, 1–10.
16. Nair, J.R.; Moots, R.J. Behcet's disease. Clin. Med. **2017**, 17, 71–77.
17. Nguyen, A.; Upadhyay, S.; Javaid, M.A.; Qureshi, A.M.; Haseeb, S.; Javed, N.; Cormier, C.; Farooq, A.; Sheikh, A.B. Behcet's Disease: An In-Depth Review about Pathogenesis, Gastrointestinal Manifestations, and Management. Inflamm. Intestig. Dis. **2021**, 6, 175–185.
18. Yazici, H.; Ugurlu, S.; Seyahi, E. Behçet syndrome: Is it one condition? Clin. Rev. Allergy Immunol. **2012**, 43, 275–280.
19. Bettiol, A.; Prisco, D.; Emmi, G. Behçet: The syndrome. Rheumatology **2020**, 1, 59.
20. Krause, I.; Yankevich, A.; Fraser, A.; Rosner, I.; Mader, R.; Zisman, D.; Boulman, N.; Rozenbaum, M.; Weinberger, A. Prevalence and clinical aspects of Behcet's disease in the north of Israel. Clin. Rheumatol. **2007**, 26, 555–560.