Anemia as a Risk Factor for Ischemic Heart Disease

Aliza Zeidman MD, Zinaida Fradin MD, Anetta Blecher MD, Howard S. Oster MD, Yoav Avrahami MD and Moshe Mittelman MD

Department of Medicine B, Rabin Medical Center (Golda-Hasharon Campus), Petah Tiqva, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: anemia, ischemic heart disease, congestive heart failure, arrhythmia

Abstract

Background: Anemia is a known risk factor for ischemic heart disease. Based on knowledge of the physiologic role of oxygen delivery to the myocardium, anemia may be a cause of more severe cardiovascular diseases or a marker of other processes occurring in the body that induce more severe disease.

Objectives: To investigate the relationship between anemia and the clinical picture of IHD, including manifestations, severity and complications.

Methods: The population studied comprised 417 similarly aged patients with IHD and anemia. The patients were categorized into subgroups of IHD according to disease severity: namely, angina pectoris, acute ischemia, acute myocardial infarction, congestive heart failure or cardiac arrhythmias. Two populations served as control groups: patients with anemia but no IHD (C-I) and patients with IHD without anemia (C-II). A standard anemia workup was conducted in all patients with IHD and anemia and a correlation was made between the hematologic parameters and the manifestations and complications of IHD.

Results: The common presenting symptom was chest pain in the study group and in C-II (94% and 86% respectively) and weakness (90%) in C-I. Patients with IHD and anemia tended to suffer from a more advanced degree of IHD (80%) compared to patients with IHD alone who had milder disease (46%). Hematologic values including hemoglobin, mean cell volume, serum iron and total iron-binding capacity correlated inversely with disease severity among anemic patients with IHD. There were significant differences between the study group and C-II regarding CHF (31% and 18% respectively) and arrhythmias (41% and 16% respectively). The mortality rate was higher in patients with IHD and anemia than in patients with IHD alone (13% and 4% respectively).

Conclusions: Anemia is a significant risk factor in IHD. It correlates with advanced IHD, CHF, rhythm disturbance and higher mortality rate. An aggressive therapeutic and preventive approach might improve the outcome of this disease

IMAJ 2004;6:16–18

Anemia has been recognized as a risk factor for ischemic heart disease [1]. The role of reduced oxygenation due to decreasing hemoglobin and hematocrit on the myocardial performance has also been studied, especially on the physiologic level [1,2]. However, the precise impact of anemia on the clinical picture of IHD, i.e., manifestations, severity and complications, has hardly been investigated. We undertook the present study in an attempt to better characterize these relations between anemia and IHD.

IHD = ischemic heart disease
CHF = congestive heart failure

Patients and Methods

The charts of all patients admitted to the Department of Medicine B, Hasharon Hospital, Petah Tiqva, Israel between January1993 and December 1997 were screened. The study group consisted of patients who were admitted for evaluation and treatment of IHD and were found to have anemia, defined as hemoglobin <12 g/dl for males and <11.5 g/dl for females.

The patients with IHD were divided into three categories: angina pectoris, acute ischemia, and acute myocardial infarction. The diagnosis was established as described in the literature [3]. All patients were further classified regarding the presence or absence of congestive heart failure. Additionally, patients with rhythm disturbance were divided into groups with supraventricular and ventricular arrhythmias.

Two groups of patients served as controls: the first consisted of 50 consecutive patients with IHD aged >65 years (age-matched population) admitted to the Department of Medicine during a 6 month period, June through December 1997, for evaluation and treatment of anemia (C-I); and the second comprised 50 consecutive patients without anemia who were admitted for IHD during December 1997 (C-II).

The anemia workup included complete blood count, routine blood chemistry, serum iron concentration, total iron-binding capacity, vitamin B_{12} and folic acid. The study groups were characterized and the correlation between IHD, its severity, its clinical manifestations and its complications (arrhythmias, CHF and in-hospital mortality), and the hematologic parameters were determined using standard statistical methods.

Statistical analysis

Two-way variance analysis was used to compare the results of the hematologic parameters in the study group and group C-I. We used Pearson's correlation test to quantify the associations between hematologic parameters and clinical presentations in the study group, as compared with group C-II. Data are expressed as mean $\pm$ SD. The accepted statistical significance was $P < 0.05$.

Results

Patient characteristics

The study group comprised 317 patients who met the criteria for both IHD and anemia during the study period. There were 134 female and 183 male patients with a mean age of 76.1 $\pm$ 4.2 years. The control group C-I (anemia without IHD) included 50 patients (27 females and 23 males), mean age 76.4 $\pm$ 6.3 years. In control

group C-II (IHD only) there were 20 female and 30 male patients, with a mean age of 73.6 ± 7.4 years.

On admission, the common symptoms in the study group were chest pain (94%), cold sweating (40%), dyspnea (38.5%), palpitations (26%), nausea (12%) and weakness (12%). The most common complaint in C-I patients was weakness (90%), while in C-II patients it was chest pain (86%). The mean hemoglobin level was 8.9 ± 1.6 g/dl in the study group as compared to 9.5 ± 1.8 g/dl in the C-I group ($P = 0.014$). Mean cell volume and serum iron concentrations were 80.6 ± 5.3 Fl and 40.7 ± 10.5 µg/dl respectively in the study group and 87.5 ± 9.2 Fl and 71 ± 58.2 g/dl respectively in the control group.

IHD subgroups

Anemia was associated with a more advanced clinical presentation of IHD: In the study group only 20% of the patients suffered from angina pectoris alone, while 44% had acute ischemia and 36% had myocardial infarction. In contrast, in the C-II group (IHD only) the subgroup percentages were 54%, 26% and 20%, respectively.

Hematologic parameters in IHD subgroups [Table 1]

The severity of IHD increased with the mean age of patients: the ages were 71.9 years in patients with angina pectoria, 74 years in acute ischemia, and 77.7 years in the myocardial infarction subgroup. The mean hemoglobin level in the three subgroups was 10.7, 8.7 and 8.2 g/dl respectively. Lower levels of hemoglobin, MCV, Fe concentration and TIBC were all associated with more severe heart disease. Serum levels of folic acid and vitamin B_{12} were not significantly different among the subgroups.

Congestive heart failure [Table 2]

CHF was diagnosed in 98 patients (31%) in the study group but in only 9 patients (18%) in control group II. The mean age of the patients who developed CHF in both groups (the study group and C-II) was higher (77.2 and 79.8 years respectively) than in patients who remained free of this complication (75.5 and 72.3 years respectively). In addition, the tendency to develop CHF increased with decreasing levels of hemoglobin, MCV, serum Fe and TIBC [Table 2].

Cardiac arrhythmias [Table 3]

Of the 317 patients in the study group, 130 (41%) developed rhythm disturbances compared with only 8 patients (16%) in the C-II group. Of these 130 patients, 75 (58%) had supraventricular arrhythmias (sinus tachycardia, atrial premature beats, atrial fibrillation), and 55 (42%) had ventricular arrhythmias (ventricular premature beats, ventricular tachycardia, ventricular fibrillation). Lower levels of hemoglobin, Fe and TIBC correlated with a greater tendency to develop ventricular as opposed to supraventricular arrhythmias.

MCV = mean cell volume
Fe = serum iron
TIBC = total iron-binding capacity

Table 1. Hematologic parameters in patients with IHD and anemia

Risk factor*	Angina pectoris subgroup (n= 63)	Acute ischemia subgroup (n=141)	Myocardial infarction subgroup (n=113)	*P* value**
Age (yrs)	71.9 ± 4.6	74 ± 3.7	77.7 ± 4.2	<0.001
Hb (g/dL)	10.7 ± 1.6	8.7 ± 1.2	8.2 ± 1.2	<0.001
MCV (Fl)	81.5 ± 4.5	80 ± 6.2	79.2 ± 5.2	0.005
Fe (µg/dl)	42.2 ± 10.1	42.4 ± 10.9	37.8 ± 9.6	<0.001
TIBC (µg/dl)	327.5 ± 47.1	315.4 ± 70.6	283.6 ± 60.4	<0.001

* Mean values
** The *P* value represents the difference between the angina pectoris and the myocardial infarction subgroups

Table 2. Hematologic parameters in patients with IHD, anemia and CHF

Parameter*	CHF (n=98)	No CHF (n=219)	*P* value
Hb (g/dl)	8.4 ± 1.6	9.1 ± 1.5	<0.001
MCV (Fl)	77.7 ± 4.7	81.4 ± 5.2	<0.001
Fe (µg/dl)	39.7 ± 10.8	41.3 ± 10.4	0.021
TIBC (µg/dl)	294.6 ± 67.9	311.8 ± 63.4	0.003

* Mean values

Table 3. Hematologic parameters and arrhythmias in patients with IHD and anemia

Parameter*	SVA (n=75)	VA (n=55)	*P* value
Hb (g/dl)	9.6 ± 2	8.2 ± 1.3	<0.001
MCV (Fl)	80.7 ± 5.6	79.8 ± 3.2	0.065
Fe (µg/dl)	42.1 ± 8.5	38.2 ± 9.2	0.0015
TIBC (µg/dl)	318.1 ± 58.1	294.4 ± 59.1	0.0025

* Mean values

Table 4. Hematologic values and in-hospital mortality in patients with IHD and anemia

Parameter*	Surviving patients	Deceased patients	*P* value
Age (yrs)	75.7 ± 4.1	78.4 ± 4.1	<0.001
Hb (g/dl)	9.0 ± 1.6	8.3 ± 1.4	<0.001
MCV (Fl)	80.8 ± 5.3	77.7 ± 5.1	0.009
Fe (µg/dl)	41.4 ± 10.5	35.9 ± 9.9	<0.001
TIBC (µg/dl)	307.6 ± 64	299.2 ± 74.3	0.044

* Mean values

In-hospital mortality [Table 4]

Forty-two of the 317 patients in the study group (13%) died during hospitalization, compared with only 2 patients (4%) in the C-II group. The causes of death were ventricular fibrillation (45%), pulmonary edema (18%), cardiogenic shock (18%), and others (19%). Patients who survived were younger (75.7 vs. 78.4 years) and had higher hemoglobin, MCV and Fe levels.

Discussion

Anemia has been shown to be an important factor in increasing cardiac output to maintain adequate oxygen supply to the tissues [1,4], and several mechanisms have been suggested: among them increased stroke volume [5] and decreased peripheral vascular

resistance [6,7]. When hemoglobin concentration is reduced to less than half the normal level, ventricular function is impaired, presumably because the coronary flow has approached its maximum [8]. Angina pectoris usually occurs in patients with underlying coronary disease [9], however in anemic patients it may occur without coronary disease because of the low hemoglobin level [10,11]. Anemia as well as IHD and systolic dysfunction have been shown to be an independent and significant risk factor for CHF recurrence [12]. However, unlike patients with myocardial disease, patients with anemia have a high cardiac output and low systemic vascular resistance and blood pressure [13]. Successful treatment of anemia is associated with significant improvement in functional class and cardiac and renal function, and a reduced need for diuretics and hospitalization [14].

In this study we attempted to determine the clinical implication of anemia in patients with IHD. Eighty percent of patients in the study group were admitted because of an ischemic event (acute ischemia and myocardial infarction), while angina pectoris alone was the main presentation in the C-II group. Our data demonstrate that anemia is associated with an increased risk to develop clinically severe IHD. Our data also confirm the association between an increased tendency to develop CHF and decreasing levels of hemoglobin.

Studies have shown that a 1 g/dl decrease in hemoglobin level is an independent, statistically significant risk factor for the development of cardiac morbidity and mortality, especially in patients with chronic renal failure [15]. The current study confirms that lower hemoglobin level is associated with increased cardiovascular mortality.

Acute myocardial infarction, similar to chronic inflammatory diseases, may be accompanied by a significant decrease of Fe and TIBC, especially during the first 3 days [16,17]. Potential mechanisms include direct damage of the vessels or an immunologic inflammatory response. An increased uptake of iron in the reticuloendothelial system for synthesis of ferritin may account for the lowered Fe level and iron saturation of tranferrin and TIBC [17,18]. We obtained similar results: patients who developed myocardial infarction had lower levels of Fe and TIBC compared with patients with angina pectoris alone. This finding further suggests a role for inflammation in the pathogenesis of myocardial infarction.

Although the statistical methods lack multivariate analysis that emphasizes the independent causes of the adverse outcomes, the present study confirms previous reports describing anemia as a risk factor for IHD. The correlation of hemoglobin, MCV, Fe and TIBC with the adverse outcomes might also be due to extensive neurohormonal and inflammatory activation, and it is possible that anemia and especially the low Fe/TIBC are not responsible for the adverse outcomes but are markers of other processes occurring in the body. Further studies are needed to determine which of these factors are markers of more severe disease and which are independent causes. At this stage, physicians should be alert to the association between anemia and cardiovascular morbidity and mortality, especially in the older population, and should consider an earlier and more aggressive therapeutic approach towards the correction and prevention of anemia.

References

1. Shulman LN, Braunwald E, Rosenthal DS. Hematological-oncological disorders and heart disease. In: Braunwald E. Heart Disease: A Textbook of Cardiovascular Medicine. 5th edn. Phildadelphia: WB Saunders, 1997:1786–808.
2. Brannon ES, Merrill AJ, Warren JV, Stead EA. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. *J Clin Invest* 1945;24:332.
3. Ganz P, Braunwald E. Coronary blood flow and myocardial ischemia. In: Braunwald E. Heart Disease: A Textbook of Cardiovascular Medicine. 5th edn. Philadelphia: WB Saunders, 1997:1161–78.
4. Eckstein RW. Development of interarterial coronary anastomoses by chronic anemia. Disappearance following correction of anemia. *Circ Res* 1955;3:306–10.
5. Florezano F, Diaz G, Regonesi C, Escobar E. Left ventricular function in chronic anemia: evidence of noncathecholamine positive inotropic factor in the serum. *Am J Cardiol* 1984;54:638–45.
6. Duke M, Abelmann WH. The hemodynamic response to chronic anemia. *Circulation* 1969;39:503–13.
7. Roy SB, Bhatia ML, Mathur VS, Virmani S Hemodynamic effects of chronic severe anemia. *Circulation* 1963;28:346–56.
8. Case RB. Berglund E, Sarnoff SJ. Ventricular function. Changes in coronary resistance and ventricular function resulting from acutely induced anemia and the effect thereon of coronary stenosis. *Am J Med* 1955;18:397–405.
9. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effect of anemia. *Am Heart J* 1972;83:415–26.
10. Elliot AH. Anemia as the cause of angina pectoris in the presence of healthy coronary arteries and aorta: report of case. *Am J Med Sci* 1934;187:185.
11. Roig E, Betriu A, Castaner A, Magrina J, Sanz G, Navarro-Lopez F. Disabling angina pectoris with normal coronary arteries in patients undergoing long-term hemodialysis. *Am J Med* 1981;71:431–4.
12. Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Partrey PS. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. *Kidney Int* 1995;47:884–90.
13. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PE, Harris PS. Pathogenesis of oedema in chronic severe anemia: studies of body water and sodium, renal function, hemodynamic variables, and plasma hormones. *Br Heart J* 1993;70:357–62.
14. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalization. *J Am Coll Cardiol* 2000;35:1737–44.
15. Eckardt KU. Cardiovascular consequences of renal anemia and erythropoietin therapy. *Nephrol Dial Transplant* 1999;14:1317–23.
16. Fitzsimons EJ, Kaplan K. Rapid drop in serum iron concentration in myocardial infarction. *Am J Clin Pathol* 1980;73:552–5.
17. Van der Schouw YT, van der Veeken PM, Kok FJ, Koster JF, Schouten EG, Hofman A. Iron status in the acute phase and six weeks after myocardial infarction. *Free Radic Biol Med* 1990;8:47–53.
18. Magnusson MK, Sigfusson N, Sigvakdason H, Johannesson GM, Magnusson S, Thorgeirsson G. Low iron-binding capacity as a risk factor for myocardial infarction. *Circulation* 1994;89:102–8.
19. Wenger NK. Special consideration in managing coronary heart disease in the elderly. *J Crit Ill* 1988;3:346–57.

Correspondence: Dr. A. Zeidman, Dept. of Medicine B, Rabin Medical Center (Golda-Hasharon Campus), P.O. Box 121, Petah Tiqva 49372, Israel.
Phone: (972-3) 937-2622)
email: alizaz@clalit.org.il