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Anemia in cardiovascular diseases

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Anemia is common in patients with heart diseases and can be presented in one third of patients with congestive heart failure and in 10% – 20% of patients with coronary heart disease. The cause of anemia in patients with heart disease is multifactorial and may include chronic inflammation, absolute and functional iron deficiency, impaired production and activity of erythropoietin, hemodilution, renal dysfunction. Hemodynamic and non-hemodynamic changes in anemia in the presence of chronic heart disease contribute to a high incidence of cardiovascular complications. Anemia is an independent risk factor for cardiovascular diseases (CVD) outcomes and probably acts as a mediator and a marker of a poor prognosis. Anemia treatment in patients with heart diseases includes erythropoiesis-stimulating agents, red blood cell transfusion, and iron replacement. Iron deficiency became a new therapeutic target and intravenous ferric carboxymaltose should be considered in symptomatic patients with systolic heart failure and iron deficiency in order to alleviate heart failure symptoms, and improve exercise capacity and life quality.

Introduction

Cardiovascular disease is a significant health problem around the world and accounts for the majority of deaths annually. Many of such patients have anemia due to acute blood loss (surgery or trauma) or chronic conditions such as renal failure or cancer.

According to the World Health Organization criteria anemia is defined in cases when hemoglobin is less than 120 g/l in females and less than 30 g/l in males. It is a major health problem that increases the mortality rate, affects physical status, and demands referral to health-care professionals. Globally, anemia affects 1.62 billion people, which corresponds to 24.8% of the total population. The highest prevalence is in preschool-age children (47.4%), and the lowest prevalence is in men (12.7%). Half of the cases are due to iron deficiency [1] which affects not only red blood cell production but also cellular functions related to muscle metabolism, mitochondrial function, neurotransmitters, DNA synthesis, and the immune system [2].

Prevalence of anemia increases with the advanced age making it a common associated comorbidity in patients with cardiovascular diseases. It has been established that anemia is an independent risk factor for cardiovascular diseases (CVD) outcomes [3].

Effects of anemia on the cardiovascular system

Understanding the physiologic response to anemia is important in order to take into account the implications of this state in regards to cardiac diseases. Three main factors are responsible for oxygen delivery to organs: blood flow and its distribution; the oxygen-carrying capacity of the blood, i.e. hemoglobin concentration; and oxygen extraction. Hypoxia in anemia is compensated through several non-hemodynamic (increased erythropoietin production to stimulate erythropoiesis, increased oxygen extraction) and hemodynamic mechanisms. The main hemodynamic factors are decreased afterload, increased preload, and positive inotropic and chronotropic effects. Enhanced nitric oxide activity, hypoxia-induced

vasodilatation and lower blood viscosity are responsible for reduced vascular resistance and lead to the decreased afterload. Chronic anemia stimulates angiogenesis and recruitment of new microvessels. Enhanced venous return (preload) and left ventricular (LV) filling lead to the increased LV end-diastolic volume and cardiac output. Increased cardiac output is responsible for arterial remodeling of the central elastic arteries such as the aorta and common carotid artery through arterial enlargement and compensatory arterial intima-media thickening, leading to the elevated systolic pressure and high inertia due to higher blood mass in the dilated arterial system. Activation of sympathetic activity enhances LV contractility, and the heart rate. Short-lasting anemia is reversible but in chronic anemia hemodynamic changes lead to cardiac enlargement and development of eccentric LV hypertrophy (LVH). It also occurs in other forms of the volume overload. In case of heart diseases chronic anemia contributes to a high incidence of cardiovascular complications [4].

Anemia in arterial hypertension

Normocytic anemia is common in hypertensive patients but more prevalent in uncontrolled hypertension. Lower hemoglobin is associated with poor blood pressure control, indicating a higher cardiovascular risk in uncontrolled hypertension [5]. It was noted that hypertensive patients with anemia had higher nocturnal systolic and mean blood pressure and a lower dipping status compared to the patients with normal hemoglobin levels. There was a trend for increased diastolic blood pressure [6].

In patients with isolated systolic hypertension and left ventricular hypertrophy lower hemoglobin was associated with the increased cardiovascular death or stroke [7].

Electrocardiographic changes in anemia

Electrocardiographic (ECG) repolarization abnormalities (ST segment depression, T wave inversion, prolonged QT) are highly prevalent in anemic patients at rest and during the tests with physical loading [8]. It has been shown that the hemoglobin level is strongly correlated with ECG changes [9].

A long ECG QT interval duration is a predictor of ventricular arrhythmia and sudden cardiac death. Hypoxia and impaired oxygen supply in anemic patients may affect repolarization of the myocardium. It has been found that anemia, macrocytosis and anisocytosis are associated with prolonged QT intervals in hypertensive patients and may contribute to the risk of sudden cardiac death [10]. Low iron stores in otherwise healthy children negatively correlated with QT and QTc intervals and may indicate some risk in developing arrhythmias [11].

Mehta et al. showed significant reproducible ST depression in anemic patients with iron deficiency during the tests with physical loading. These electrophysiological changes were corrected after iron therapy, even before the rise of hemoglobin occurred, which may be explained by the effect of iron on the tissue level [12].

Anemia in Ischemic Heard Disease

Myocardial ischemia is defined as oxygen delivery that is insufficient to meet oxygen requirements. The determinants of myocardial oxygen demand are wall tension, heart rate and contractility. The determinants of myocardial oxygen delivery are arterial oxygen content and coronary arterial blood flow. The increase of oxygen delivery in response to the enhancement of oxygen demand occurs through the changes in coronary vascular resistance, as the extraction ratio of myocardium at rest is nearly 90% [13]. Patients without coronary artery disease, therefore, have a tremendous ability to compensate the decrease in coronary arterial oxygen content through distal vasodilatation but in the presence of coronary stenosis this compensatory mechanism has a limited ability.

It was proved that anemic animals have the increased infarct size, decreased cardiac function and the survival rate in case of acute myocardial infarction (MI). Transfusion of fresh blood to anemic animals up to 100 g/L Hb reduced the infarct size and improved the cardiac function. However, blood transfusion up to 120 g/L Hb was associated with larger infarcts [14].

Sabatine et al. found out a U-shaped relationship with clinical events by the 30th day: in patients with ST-elevation MI; the mortality rate was higher in those with the hemoglobin levels below 140g/L or above 170g/L, while in patients with non-ST elevation acute coronary syndrome (ACS), death, infarction and ischemia increased in case when hemoglobin levels were below 110g/L or above 160/L [15].

Anemia is a risk factor for ischemic heart disease. Patients with ischemic heard disease (IHD) and anemia have a more advanced degree of ischemic heart disease compared to patients with isolated IHD. In anemic patients with IHD the level of hemoglobin, serum iron and total iron-binding capacity negatively correlated with the severity of IHD [16]. The mortality rate in anemic patients with IHD was higher than in patients with isolated IHD [16]. Anemia was an independent predictor of acute coronary syndrome based on the hemoglobin level, while both anemia and a high hematocrit level were predictors of myocardial infarction based on hematocrit [17].

The investigations made by Ferreira et al. revealed that hemoglobin<108g/L was one of the strongest independent predictors of one-year mortality in population with acute coronary syndrome (ACS). He suggested including the hemoglobin level in risk stratification scores of patients admitted for ACS, given that it is an easy parameter to measure and is systematically assessed at admission [18].

In the Cadilac trial anemia was common in patients with AMI who underwent primary PCI and was strongly associated with the adverse outcomes and increased mortality [19]. Anemia was an independent predictor of in-hospital mortality by the end of the first year [19].

Severe anemia can lead to disbalance between oxygen delivery and demand in the myocardium even in patients without coronary stenosis. Bailey D et al. reported a case of the ST segment elevation myocardial infarction (STEMI) secondary to severe anemia which occurred in the absence of angiographically significant coronary artery stenosis, thrombosis or coronary artery spasm [20].

Thus, there are a number of reasons for the worse outcomes in anemic patients with the obstructive coronary artery disease. Diminished oxygen-carrying capacity, activation of the sympathetic nervous system can increase myocardial oxygen demand and worsen ischemia.

Anemia in Heart Failure

Anemia is a very common comorbidity in chronic heart failure. Anemic patients are elderly women with more advanced symptoms and signs of heart failure, greater functional impairment and a higher hospitalization rate; they have a history of diabetes mellitus, renal insufficiency, and hypertension [21]. Anemia is a powerful predictor of rehospitalization rates and survival in case of chronic heart failure [22]. The prevalence of anemia increases with the severity of heart failure (HF) and can reach 79.1% in those with Class IV according to the classification of the New York Heart Association [23].

Etiology of anemia in HF may be multifactorial and a number of potential mechanisms may be responsible for such a condition in heart failure. Neurohormonal and inflammatory activation, renal dysfunction, bone marrow hyporesponsiveness, malnutrition, drug effects contribute to its development. Increased circulating proinflammatory cytokines enable defective iron mobilization, inappropriate erythropoietin production, depressed bone marrow function. Activation of the renin-angiotensin-aldosteron system, decreased renal perfusion caused by the low blood pressure and stroke volume stimulate the release of erythropoietin but the response is blunted due to effect of the circulatory cytokines. Poor nutrition due to anorexia, gastrointestinal malabsorbtion and aspirin use may precipitate iron deficiency anemia. Hemodilution can contribute to anemia. The use of the angiotensin-converting enzyme (ACE) inhibitor therapy may reduce secretion of erythropoietin [24].

Iron deficiency (ID) is the most frequent cause of anemia in patients with HF [25, 26] and can be revealed in ~46% of non-anemic patients with stable systolic HF [27].

Iron deficiency may exist in absolute or functional forms. Absolute iron deficiency occurs when total body iron stores become exhausted and ID anemia can be considered as the final phase of iron stores depletion; functional iron deficiency refers to inadequate iron release in response to the demands of the bone marrow. Functional iron deficiency can be seen in many acute and chronic inflammatory states. ID is associated with the worsening of symptoms in patients with heart failure, impaired life quality, the increased mortality and hospitalization level [28, 29, 30].

Activation of sympathetic and renin-angiotensin-aldosteron systems, chronic inflammation, absolute and functional iron deficiency, impaired production and activity of erythropoietin, hemodilution, renal dysfunction impair prognosis in heart failure patients. Probably, anemia acts as a mediator and a marker of a poor prognosis in HF patients.

Treatment of anemia in patients with heart diseases

Anemia treatment strategies in heart failure and CHD patients include erythropoiesis-stimulating agents (ESAs), red blood cell transfusions and iron replacement in iron deficient patients with or without anemia.

Sixteen randomized, controlled trials assessed the impact of ESAs in patients with heart disease. Most of these studies included patients with CHF and the reduced systolic function. Overall, moderate-quality evidence showed no benefit from ESAs in regard to improving exercise tolerance and duration or quality of life, and high-quality evidence showed no mortality benefit [31]. Serious harmful effects associated with the treatment include mortality and vascular thrombosis [31]. So, the damage outweighs the benefits in treatment of patients with mild to moderate anemia using ESAs. Although anemia is common in patients with CHF and CHD, treatment with ESAs did not decrease mortality, cardiovascular events or hospitalization rates [31]. The American College of Physicians does not recommend using erythropoiesis-stimulating agents to patients with mild to moderate anemia and congestive heart failure or coronary heart disease [31].

Blood transfusion has been suggested to correct severe anemia in patients with coronary artery disease, but data in regard to its effectiveness are contradictory. In the majority of studies investigating different transfusion protocols, a liberal blood transfusion strategy was defined as any red blood cell transfusion at a hemoglobin level up to 90 g/L, while a restrictive blood transfusion strategy was defined as any transfusion at a hemoglobin level up to 70 g/L. A meta-analysis of 10 studies totaling 203 665 patients with acute coronary syndrome (both STEMI and NSTEMI-ACS) reported that blood transfusion or a liberal transfusion strategy was associated with the increased all-cause mortality, compared with no blood transfusion or a restrictive transfusion strategy [32]. However, a transfusion or liberal transfusion strategy was associated with a significantly higher mortality risk by the 30th day only in case when a nadir hematocrit is more than 25% [32].

However, low-quality evidence data demonstrate that blood transfusion using restrictive compared with liberal transfusion protocols had no effect on mortality in patients with CHD. Observational studies suggested that transfusion is not beneficial and may be harmful for patients with heart disease and hemoglobin levels of more than 100 g/L (31). A pilot trial of 110 patients with acute coronary syndrome or stable angina undergoing cardiac catheterization and hemoglobin <100 g/L revealed a trend of fewer major cardiac events and deaths in patients with the liberal transfusion strategy as compared with a more restrictive strategy [33].

Due to inconsistent results of the studies and the lack of adequately powered RCTs restrictive red blood cell transfusion strategy may be considered in the settings of ACS and for hospitalized patients with coronary heart disease [31, 34].

Benefits of using intravenous iron injections in treatment of iron deficiency with or without anemia in HF patients

Iron has several vital functions in the body. It serves as a carrier of oxygen to the tissues, a transport medium for electrons within cells, and an integrated part of important enzyme systems in various tissues. Several iron-containing enzymes act as electron carriers within the cell and their role in the oxidative metabolism is to transfer energy within the cell and mitochondria. Other key functions for the iron-containing enzymes (e.g. cytochrome P450) include synthesis of steroid hormones and bile acids; detoxification of foreign substances in the liver; and signal controlling in some neurotransmitters, such as the dopamine and serotonin systems in the brain [5].

Few studies addressed to intravenous iron therapy for patients with heart disease. Data from Fair-HF study, which included patients with and without anemia demonstrated, that 27.6% of patients treated with intravenous iron carboxymaltose had cardiovascular events compared with 50.2% of patients receiving placebo (p=0.01). Moderate-quality evidence showed that intravenous iron administration increased exercise tolerance and duration in patients with stable CHF including patients with Stage 3 chronic kidney disease. FAIR-HF trial (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) included anemic and nonanemic patients, with the majority of them having ferritin levels less than 100 μg/L [36]. This trial showed that 200 mg of intravenous ferric carboxymaltose (FCM) increased a 6-minute walk distance (313 m vs. 277 m) compared with intravenous

saline [36]. Moderate-quality evidence showed that intravenous iron improved quality of life in patients with anemia or iron deficiency, stable CHF, and chronic kidney disease excluding the patients with the 4th and 5th stages. The FAIR-HF study showed that intravenous iron treatment improved Patient Global Assessment scores compared with control patients and the improved NYHA functional class, regardless of the anemia status (hemoglobin level ≤120 g/L) [36]. This trial also showed improved life quality. [36]. There was no statistically significant difference in serious harmful effects between the intravenous iron treatment and the control groups [36].

The CONFIRM-HF trial was aimed at studying effects of long-term intravenous iron therapy in ferric carboxymaltose inpatients with symptomatic heart failure and iron deficiency. Totally 304 patients with stable ambulatory HF (class II or III according to New York Heart Association (NYHA) classification) and left ventricular ejection fraction (LVEF) ≤45%, elevated natriuretic peptides (brain natriuretic peptide >100 pg/mL and/or N-terminal-pro-brain natriuretic peptide>400 pg/mL), presence of ID (defined as serum ferritin level <100 ng/mL, or between 100 and 300 ng/mL if transferrin saturation was <20%) and hemoglobin (Hb) up to15 g/L were enrolled in the study. This study showed that treatment of stable, symptomatic, 'iron-deficient HF patients with intravenous iron (FCM) results in sustainable improvement of functional capacity as measured over a 1-year period using the 6-MWT walking test, improvement in quality of life, significantly reduced risk of hospital admission due to worsening of HF during a1-year follow-up period. These favorable results were consistent across all pre-specified subgroups including patients with and without anemia [37].

The results of CONFIRM-HF compared with FAIR-HF had a more objective primary end-point, documented longer-term sustainability of beneficial effects of treatment with FCM and the acceptable safety profile (i.e. 12 months compared with 6 months or less in previous studies) and provided data on significant risk reduction of the hospitalization due to HF worsening [37].

A meta-analysis of all randomized controlled trials that investigated the effects of intravenous iron therapy in iron-deficient patients with systolic HF (also analyzed separately in anemic and non-anemic subjects) showed that intravenous iron therapy in patients with systolic HF and ID reduced the risk of the combined endpoint of all-cause death or cardiovascular hospitalization, the risk of the combined endpoint of cardiovascular death or hospitalization due to advanced HF. However there was no effect on either all-cause or cardiovascular mortality, parenteral iron therapy resulted in the improved exercise capacity (as reflected by a longer 6MWT distance) and life quality, and also in alleviation of HF symptoms (reduction in the NYHA class) [38].

Intravenous FCM should be considered in symptomatic patients with systolic heart failure and iron deficiency (serum ferritin level <100 ng/mL, or between 100 and 300 ng/mL if transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and life quality [39].

Conclusion

Management of patients with heart disease and anemia might appropriately differ from that of the general population. Hence, clinical judgment and understanding the evidence base are critical when managing these patients. Anemia is associated with worse outcomes in patients with cardiovascular diseases. However, it is uncertain if anemia is the cause or the marker of poor outcomes and thus it only reflects advanced cardiovascular disease. НК

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