Anemia and erythropoietin in cardiovascular disease
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Chapter 1

Introduction and aim of the thesis
Cardiovascular disease (CVD) is to date the number one cause of death worldwide, accounting for almost 30% of all global deaths. Despite development of novel therapeutics it is projected that death from CVD will increase to 23.3 million in 2030. Major disorders in the group of CVD include coronary heart disease, cerebrovascular disease, congenital heart disease and thrombotic and embolic disease. Eventually, cardiovascular disease can cause a state of heart failure (HF), a complex of symptoms related to impaired cardiac function. The Framingham study showed that the current lifetime risk to develop heart failure is 1 on 5.

**Anemia and cardiovascular disease**

Anemia is an important co-morbidity which is frequently observed in patients with cardiovascular disease. Most commonly it is defined by decrease of hemoglobin as a reflection of the pathological state of reduced circulating red blood cells. Its presence in patients with cardiovascular disease has been associated with significantly impaired morbidity and mortality and therefore understanding its cause is of clinical relevance. Causes of anemia generally divide in decreased production, increased destruction or loss of red blood cells. In cardiovascular disease, anemia is caused mainly by decreased production of red blood cells. Under normal conditions, a hormone to maintain hemoglobin at a constant level, erythropoietin (EPO) is secreted in response to low oxygen levels in the kidney. This in turn causes erythrocyte maturation and growth. Several factors are associated with decreased red blood cell production. The renin-angiotensin-aldosterone-system (RAAS) is frequently activated in patients with cardiovascular disease due to hypoperfusion. This subsequently causes renal vasoconstriction in order to maintain its filtration rate. Fluid retention occurs, as a result of vasopressin and antidiuretic hormone, leading to hemodilution. Other less well understood causes in cardiovascular disease are iron deficiency and bone marrow impairment, although the latter can be caused by bone marrow resistance to erythropoietin. This is further fuelled by the observation of disproportionally high erythropoietin levels in heart failure patients. These may be explained by either anemia, RAAS activation and increased levels of inflammatory factors.

**Erythropoietin in cardiovascular disease**

Discovered first as hematopoietine in patients with high red blood cell counts living on height, its name was replaced by erythropoietin in 1948. After purification and cloning of the hormone, its use was first registered for patients with renal anemia. As more patients were using erythropoietin, patients treated with the hormone showed increase
in cardiac function. With the discovery of the erythropoietin receptor in different organs than the red bone marrow, it was hypothesized that erythropoietin could possess non-erythropoietic effects as well. Indeed, in experimental settings, erythropoietin decreased myocardial infarct size in experiments of ischemia and reperfusion. Second, erythropoietin improved cardiac function in models of experimental heart failure independent of infarct size through increasing capillary to myocyte ratio. Eventually, the mechanism of erythropoietin was found due to mediated by upregulation of vascular endothelial growth factor (VEGF) and increased endothelial progenitor cells, leading to this increased capillary density and increased cardiac performance.

Furthermore, erythropoietin was responsible for decrease in apoptosis of cardiomyocytes exposed to ischemia. To date, several large clinical studies have been performed to assess erythropoietin treatment to either preserve cardiac function or correct anemia in an attempt to increase cardiac function and reduce mortality and morbidity. The results of these trials will be discussed in this thesis and put into perspective.

Aims of this thesis
The first part of the current thesis is focused on the etiology of anemia in patients with cardiovascular disease, including coronary artery disease, heart failure and patients undergoing coronary artery bypass graft (CABG) surgery. In chapter 2 we studied the correlation between hemodynamic parameters and hemoglobin levels in a broad spectrum of cardiovascular patients. Chapter 3 focuses on inflammation in patients with chronic heart failure. Heart failure is characterized by increase levels of cytokines, which may influence erythropoiesis and EPO production. In this chapter we establish the association between anemia and inflammation in heart failure patients. In chapter 4 we studied the prognostic significance of sustained post-operative anemia in patients following CABG surgery and the role of RAAS inhibition in this process. In chapter 5 we tried to further elucidate the relation between inflammation and anemia. Therefore we studied the association between the bone marrow response (reticulocyte count) to anemia and inflammation in patients before and after CABG surgery.

The second part comprises the role of erythropoietin treatment in CVD. In chapter 6 we discuss the potential role of erythropoietin in heart failure patients based on a recently published meta-analysis. During short term follow up there was a trend towards lower event rate in patients with acute MI treated with erythropoietin. In chapter 7 we present the long term effects of erythropoietin on cardiovascular endpoints. In chapter 8 we give comments on the current state of erythropoietin therapy in heart failure patients. Chapter 9 summarizes this thesis and provides future perspectives on the origin and treatment of anemia in patients with CVD.
References


Part 1  | Anemia in cardiovascular disease