Anemia and erythropoietin in cardiovascular disease
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Chapter 9

Summary, conclusions and future directions
Anemia is an established risk factor for mortality and morbidity in patients with cardiovascular disease. As the impact of cardiovascular disease on hospitalization, mortality and economic burden is enormous, new treatment regimens are warranted. Understanding the pathophysiological processes involved in the anemia of cardiovascular disease may reveal novel therapeutic options. One of the therapeutics currently under investigation is erythropoietin (EPO), a hematopoietic hormone that has extra-hematopoietic effects as well. In chapter 1 we discuss the current knowledge concerning the etiology of anemia and the role of EPO in cardiovascular disease and provide a rationale for the aims of the current thesis. The current thesis aims to explore the etiology of anemia in cardiovascular disease and to evaluate EPO treatment.

Anemia and cardiovascular disease

Several factors play a role in the etiology of anemia in patients with cardiovascular disease. In the first part of this thesis we investigated the role of congestion, inflammation and angiotensin converting enzyme (ACE) inhibitors in patients with cardiovascular disease. First, we aimed to assess central venous pressure in a broad spectrum of cardiovascular patients. In chapter 2 we evaluated the role of inflammation in the presence of anemia in chronic heart failure patients. In 325 patients, levels of inflammatory factors interleukin-6, soluble tumor necrosis factor receptor 1 and high sensitive C-reactive protein and hemoglobin were assessed. In this heart failure cohort, 40% of the patients were anemic. Anemic patients had significant higher levels of interleukin-6, high sensitive C-reactive protein and soluble Tumor Necrosis Factor Receptor 1. In multivariable analysis, higher levels of high sensitive C-reactive protein and soluble Tumor Necrosis Factor Receptor 1 were significantly associated with anemia. Cox regression analysis revealed soluble Tumor Necrosis Factor Receptor 1 as a significant predictor of mortality. From these data we may conclude that these inflammatory cytokines, could be responsible for the development of anemia in heart failure patients and play a significant role in the mortality of
heart failure patients in the presence of anemia. Despite all efforts to prevent post-operative anemia, more than 90% of patients develop anemia after coronary artery bypass grafting (CABG) surgery. These cardiovascular patients are thus subjected to an established cardiovascular risk factor by an intervention that is intended to reduce that risk. In chapter 4 we evaluated whether the severity and the degree of postoperative anemia affects prognosis in a cohort of 2553 stable patients with left ventricular ejection fraction >40%, two to seven days after scheduled CABG who were randomized between the ACE inhibitor Acupril or placebo. In 43% of the patients, anemia persisted for more than 50 days. These patients with sustained post-operative anemia displayed a markedly impaired prognosis. In fact, every mg/L decrease in hemoglobin was associated with an 11% increase in the primary composite endpoint of death, myocardial infarction, stroke, heart failure and angina. Furthermore, patients randomized to Acupril had slower recovery of hemoglobin levels. We concluded that postoperative anemia is common, frequently persists for months after CABG surgery and is associated with an impaired outcome. In patients with anemia, ACE inhibitors slowed recovery from postoperative anemia and increased the incidence of cardiovascular events after CABG surgery.

To further explore whether bone marrow dysfunction could be responsible for prolonged postoperative anemia we analyzed reticulocyte count and biochemical markers in a cohort of 1147 patients who underwent scheduled CABG surgery. The increase in reticulocyte count after CABG surgery was inversely related to changes hemoglobin and C-reactive protein. In 11% of the patients, reticulocyte count did not increase following the anemic state of surgery. We observed that impaired erythropoiesis after CABG surgery is associated with an increased inflammatory response. This could be a clue in the etiology of sustained impaired erythropoiesis response following thoracic surgery.

**Erythropoietin in cardiovascular disease**

Several studies have evaluated the treatment of EPO in cardiovascular patients. First, in experimental setting EPO not only showed to have hematopoietic effects but cardio-protective pleiotropic effects as well in animals subjected to myocardial infarction. Both anti-apoptotic properties and neovascularisation owe to these effects. In clinical trials however, EPO therapy does not results in beneficial cardiac remodeling. One of these studies performed to evaluate EPO to preserve cardiac function was the HEBE III study. As EPO therapy could actually result in thromboembolic events due to increased blood viscosity, we performed a one year follow up to evaluate readmissions and thrombo-
embolic events in the HEBEIII study. In total, of the 529 patients, 485 patients had complete follow up. The composite end point of all-cause mortality, re-infarction, target vessel revascularization, stroke and/or heart failure was comparable between the treatment groups. Furthermore, there was a comparable incidence of thromboembolic complications in both treatment groups, suggesting that EPO treatment is safe at long term.

A further concern to treatment with EPO was raised in patients with heart failure. Depending on the definition used, up to 40% of these patients are anemic. As the presence of anemia in these patients is associated with morbidity, mortality and functional status, correcting anemia to improve outcomes seems plausible. In contrast to a single bolus of EPO in studies evaluating this drug in patients with myocardial infarction, frequent administration is needed in patients with anemia in heart failure. This raised the question whether rheologic effects of EPO could actually induce harm as higher blood viscosity could lead to thromboembolic events. In the chapter 6 we give comment on these possible effects and the therapeutic window of erythropoietin. In 2013, the long awaited RED-HF trial was published. In this randomized, double-blind trial, 2278 patients with systolic heart failure and mild-to-moderate anemia (hemoglobin level, 9.0 to 12.0 g per deciliter) were randomized to receive either darbepoetin alfa (to achieve a hemoglobin target of 13 g per deciliter) or placebo. The primary outcome was a composite of death from any cause or hospitalization for worsening heart failure. Small studies had already shown a beneficial effect, although trials with EPO in non-cardiac studies showed an increase in thromboembolic events. No differences could be observed in the primary endpoint. Patients treated with darbepoetin did however have an improvement in quality of life. In chapter 8 we comment on the RED-HF study.

**Future directions**

In the last decade, anemia has been increasingly recognized as a therapeutic target in cardiovascular patients to improve survival and quality of life. Neutral results of the large phase 3 trial RED-HF indicate however, that other avenues should be explored. Although multiple mechanisms attribute to anemia in cardiovascular patients, work from this thesis indicates that inflammation and fluid retention are important and prognostic relevant etiologies for anemia in the cardiovascular patient, suggesting that therapeutic targets focusing on these entities might prove beneficial.
Summary, conclusions and future directions

Inflammation
In the nineties, tumor necrosis factor alpha (TNF-α) was discovered as an important biomarker in patients with heart failure. As it seemed to be involved in unfavorable remodeling, clinical trials with a TNF-α inhibitor (infliximab) in patients with heart failure followed subsequent. Despite the therapeutic promise, infliximab adversely affected patients with moderate to severe heart failure, despite effectively lowering TNF-α and interleukin 6,10,11. Recent studies also showed that patients with myocardial infarction who were administered infliximab did not have clinical benefit.12 These trials unfortunately did not assess hemoglobin or anemia. Other trials investigating infliximab in patients with other chronic disease, rheumatoid arthritis and inflammatory bowel disease, did however reveal an improvement in hemoglobin levels, suggesting that TNF alpha inhibition could be an effective treatment for the anemia of chronic disease.13,14 The paradoxal results of the earlier studies with infliximab in patients with heart failure could be explained by a recent discovery. Experimental data reveals that two isoforms of the tumor necrosis factor receptor posses different effects. Myocardial injury is mediated by the tumor necrosis factor receptor type 1, whereas beneficial effects are mediated trough the tumor necrosis factor receptor type 2.15 Infliximab, which does not selectively inhibit one of these receptors, thus has ambivalent effects. Future studies should be aimed to explore the mechanism of the tumor necrosis factor receptor type 1, and the effects of its selective inhibition on anemia and cardiovascular disease.

Congestion
Fluid congestion is a hallmark symptom of the heart failure syndrome. Increasing venous pressure causes fluid to transude out of capillaries into tissue spaces faster than lymphatics can drain the fluid away, eventually causing edema. In chronic heart failure, decreased renal perfusion causes activation of the renin-angiotensin alosterone system (RAAS), resulting in fluid retention and increase in extracellular volume. Furthermore, increased levels of antidiuretic hormone may lead to fluid retention. Eventually, this fluid overload causes hemodilution, resulting in a state of pseudoanemia.16,17 Despite the relation between anemia and fluid retention, signs and symptoms were absent in these studies. It thus seems that hemodilution precedes clinical presentation of fluid overload. In this thesis we additionally show that when anemia is present on top of increased venous pressure, patients have a twofold risk of mortality, further underlining that anemia is marker of severity of disease. Studies investigating and targeting fluid retention are therefore warranted. A study with direct measurement of blood volume and additionally guided therapy using novel radiolabeled dye dilution techniques is
currently tested in the ongoing TEAM-HF (Treating to Euvolemia by Clinical Assessment and Measured Blood Volume in Heart Failure) trial.\textsuperscript{18} Another important anemia related therapeutic target is iron deficiency. Even independent of the presence of anemia, iron deficiency is related to impaired quality of life and prognosis.\textsuperscript{19} Iron is not only an important integral component of hemoglobin, it is important in oxygen storage in myoglobin and cellular energy production in muscles.\textsuperscript{20,21} Therefore, iron suppletion is proposed as an important therapeutic target independent of anemia or as an alternative to erythropoiesis stimulating agents such as EPO.\textsuperscript{19} Indeed, in the FAIR-HF trial, iron repletion resulted in improvement of functional capacity and quality of life.\textsuperscript{22} With neutral effects of the RED-HF, one could therefore speculate whether anemia is only a marker of vulnerable heart failure patients. Furthermore, iron metabolism could be a major link between anemia and inflammation as proinflammatory cytokines are involved in the synthesis of hepcidin, a hormone that in turn regulates intestinal iron absorption and tissue distribution by inducing degradation of the cellular iron exporter ferroportin.\textsuperscript{23,24} Future research could thus focus on these mediators. Several trials are currently investigating iron suppletion on outcome in heart failure patients.

In the current thesis we provide evidence to support the notion that sustained postoperative anemia should not be considered as a benign disease as mortality rates are doubled. Therefore, standard diagnostic evaluation and treatment of anemia before discharge might improve outcome after CABG. In addition, increased utilization of contemporary strategies to prevent allogenic blood transfusions, such as minimal invasive surgery, autologous blood transfusions, thrombostatic drugs and erythropoiesis stimulating proteins might limit postoperative anemia. Alternatively, sustained postoperative anemia might represent a marker for a high risk population. Second, patients scheduled for CABG surgery with active chronic inflammation could represent an even higher risk group and especially these patients should be intensively monitored to limit the duration of post-operative anemia after CABG surgery. In addition, it would be prudent to avoid erythropoiesis inhibiting factors such as angiotensin converting enzyme (ACE) inhibitors in the early post operative phase.\textsuperscript{25} Finally, it seems that anemia is a marker of disease rather than a mediator and therefore identifies the vulnerable cardiovascular patient. First, anemia should be recognized as such and proper evaluation including hematinc deficiencies and reticulocytes should be performed in order to improve morbidity.\textsuperscript{26} Second, new studies are needed to investigate mechanistic causes of anemia in cardiovascular patients to improve morbidity and mortality.
Erythropoeitin and cardiovascular disease

Recombinant EPO has been used for over three decades in patients with chronic kidney disease, resulting in improved quality of life and decrease in blood transfusions. It was increasingly recognized as a pleiotropic cytokine in 2002. In experimental setting EPO improved infarct size and left ventricular function following myocardial infarction. The first clinical studies with EPO treatment in heart failure were promising and treatment was safe. EPO treatment showed a trend towards reduction in mortality and first hospitalizations for heart failure. These observations were contradictory to other patients groups in which EPO treatment was investigated. In patients with acute ischemic stroke for example, EPO was associated with a higher death rate. Furthermore, in the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) study, patients with chronic kidney disease had increased risk of stroke. In a subanalysis of the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) study, also performed in patients with chronic kidney disease, uptitration of EPO to higher levels of hemoglobin resulted in increased risk of death, myocardial infarction, congestive heart failure or stroke. In the RED-HF study, chronic treatment with erythropoietin did result in more frequent thromboembolic events, although stroke did not occur more often in the EPO group. In myocardial infarction, however, a single bolus of EPO did not result in more major adverse events. In addition, in this thesis we show that up to 1 year after administration, a single bolus of EPO is safe. From these data we can speculate that timing and dosage of EPO is crucial with regard to effects and adverse effects. However, trials using low dose EPO are currently not available, it could thus be that EPO is still effective, but should be administered in lower doses. On the other hand, new erythropoietin derivates are being developed that do not possess hematopoietic effects. These non-erythropoietic derivates retain the tissue protective properties without undesirable effects of erythropoiesis. Especially in chronic use these agents would be desirable. A recent experiment study showed that treatment with a small peptide sequence within the EPO molecule, helix B surface peptide, shows cardioprotection. However, this agent is only studied by one study group, and clinical studies are lacking so far.

Results from the experimental EPO studies do not translate to the human setting. Several factors could be involved in these discordant results. For instance coronary anatomy of rodents is different than in humans, possibly also resulting in far larger infarct sizes in the experimental studies. Second, experimental studies do not take co morbidities and medication use into account. Dosage of erythropoietin is also different then in experimental setting, as higher cumulative doses of EPO were used. Finally, whereas EPO
could be administered directly following myocardial infarction in experimental setting, in human setting EPO could only be administered after a median time of four hours after onset of symptoms in the case of myocardial infarction. These factors should make us be cautious with interpreting experimental work into clinical setting.

Putting the knowledge of the current thesis and recent literature in perspective, it seems that anemia is merely a marker of severity of disease and that EPO, although effective in experimental setting does not translate into clinical application to either prevent myocardial damage in patients with myocardial infarction or improve prognosis in patients with heart failure.

In summary, the present thesis aimed to investigate associated factors for the development of anemia in cardiovascular disease and evaluate the therapeutic potential of EPO. Results from our study showed that fluid retention, inflammatory factors and bone marrow dysfunction could play an important role in the development of anemia in patients with heart failure, or following CABG surgery. Furthermore, our results show that a single bolus of EPO following myocardial infarction is safe. Future studies evaluating inflammation, volume status and other mediators of anemia in cardiovascular disease are warranted. Therapy of EPO in patients with heart failure or following myocardial infarction seems past, although knowledge of the mechanism of cardioprotection will lead to novel agents for the future.
References


Summary, conclusions and future directions


