# TRANSFUSION MEDICINE UPDATE

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# Anemia in CHF: Does Transfusion Help or Harm?

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## *INTRODUCTION*

Patients with advanced congestive heart failure commonly become anemic, and the literature provides ample evidence that anemia in CHF is associated with adverse outcomes.

Use of erythropoietin in this population increases hemoglobin levels and subsequently improves ventricular function. These observations lead some clinicians to conclude that correction of anemia via transfusion must also be beneficial. Notably, however, there is scant literature supporting the idea that red cell transfusion confers such a benefit in any form of heart disease,[1,2] whereas there is abundant evidence to the contrary.[3-7] This Transfusion Medicine Update describes recent advances in understanding the pathophysiology of anemia in CHF, the risks and benefits of PRBC transfusion, and some previously unappreciated benefits of erythropoietin therapy in CHF.

## *THE CARDIO-RENAL-ANEMIA SYNDROME*

The cardio-renal-anemia syndrome is a relatively new but important concept in CHF pathophysiology.[8,9,10] This entity is a complex vicious cycle of congestive heart failure, chronic renal disease, and anemia each compounding the severity of the others via numerous mechanisms, some long understood, and others newly realized. Anemia in CHF has multiple causes, as well as, multiple effects.

Ventricular dysfunction comprises not only "backward" failure producing generalized edema and hypervolemia with hemodilution, but also "forward" failure with hypo-perfusion and ischemic damage to critical organs including the kidney. Advancing renal failure produces not only uremia and accelerated atherosclerosis, but also decreases erythropoietin production, and may be aggravated by angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). These drugs also may suppress erythropoiesis, thus aggravating similar effects of inflammatory cytokines, which are already elevated in CHF. Uremia produces platelet dysfunction, which may aggravate aspirin-induced gastric bleeding. Bowel edema and the general debility of CHF lead to malnutrition and poor iron and vitamin absorption.

This multi-factorial anemia reduces oxygen carrying capacity, and if severe enough, further stresses the compromised heart even as it tries to beat faster and harder to compensate. It is at this arc of the vicious cycle that clinicians commonly suppose that erythropoietin therapy helps matters, and where they may be tempted to intervene with PRBC transfusion instead. However, the picture is not quite so simple.

## *BENEFITS OF ERYTHROPOIETIN*

Recent research suggests that erythropoietin itself does much more than stimulate erythropoiesis.[8,9,10] Erythropoietin suppresses cardiomyocyte apoptosis and stimulates angiogenesis and neovascularization following injury. It may also suppress cytokine-mediated inflammation. Thus, it may be that when erythropoietin levels fall with advancing renal failure, its cardio-protective effects are withdrawn, although these may be restored with therapeutic EPO administration. If so, low hemoglobin levels attributable to low erythropoietin, as well as, improved hemoglobin levels due to EPO therapy may actually be side issues; in other words, cardiac function may depend less on the hemoglobin level *per se* than on the erythropoietin level.

## *RBC TRANSFUSION IN CHF*

Transfused stored blood lacks the cardioprotective properties of erythropoietin and may have deleterious effects. Besides acutely increasing circulating volume and viscosity, stored red cells have reduced levels of 2,3 DPG when initially transfused and thus release oxygen to tissues less efficiently. Stored RBCs also lose nitric oxide, and may function as nitric oxide "sinks" when transfused, promoting vasoconstriction, platelet aggregation and ineffective oxygen delivery. Transfused blood may introduce cytokines released during storage, with potential exacerbation of myocardial ischemia. Finally, red cell transfusion of course depresses erythropoietin secretion, further depriving the myocardium of this surprisingly versatile protective hormone. These drawbacks are in addition to the usually cited hazards of transfusion: transfusion-transmitted infections and sepsis, Transfusion-Related Acute Lung Injury (TRALI), hemolytic transfusion reactions, febrile reactions and allergic reactions, any of which are poorly tolerated in CHF.

Various observational, retrospective, and randomized prospective studies, [3-7] have examined outcomes in transfused cardiac patients, finding that restrictive (as compared to liberal) transfusion strategies produce at least equivalent, and often superior, results in such measures as 30 and 60 day mortality, length of stay, risk of MI, and need for inotropic drugs, balloon pump therapy, or even return to bypass following CABG surgery. For all these reasons, it is critical to distinguish between near-normal hemoglobin levels due to natural or administered erythropoietin versus those achieved by transfusion.

Despite its drawbacks, transfusion is sometimes unavoidable: severely anemic patients who remain symptomatic despite adequate volume repletion, oxygenation and ancillary therapy cannot wait for the effects of erythropoietin. This is a matter of clinical judgment. Nevertheless, there is broad agreement in the literature that many categories of patients with hemoglobin levels of at least 7 g/dL appear to do at least as well as equivalent patients maintained at higher levels via transfusion.[4,5]

The issue of transfusion triggers in acute coronary syndromes remains unsettled, and higher transfusion triggers (hemoglobin 9g/dL or greater) are still frequently advocated.[11] This uncertainty is due more to lack of data than to actual evidence that higher triggers produce better outcomes.[1,3] More studies are needed in this area.

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