Blunted Erythropoietin Production and Defective Iron Supply as Erythropoietin Production as Major Causes of Anemia in Patients With Chronic Heart Failure

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BACKGROUND Recent studies have shown that anemia is a common comorbid condition in patients with chronic heart failure (CHF), suggesting an impact on history and prognosis. Aim To investigate the mechanisms of anemia in a series of consecutive anemic CHF patients and define a rational therapeutic approach.

METHODS A series of 148 consecutive adult CHF pts with Hb <13 g/dl (males) or <12 g/dl (females) was studied. Potential responsible factors for anemia were investigated by evaluating endogenous erythropoietin (Epo) production, serum cytokine levels (TNF-alpha and its soluble receptors, IL-6 and IL-1Ra), body iron status, and iron supply for erythropoiesis.

RESULTS 105 pts (71%) had evidence of severe defective endogenous erythropoietin production, indicated by an observed/predicted log(serum Epo) ratio <0.8; 85 pts (57%) had low serum iron (mean value for men 105, for women 45 nmol/L; 61% (47) had low transferrin saturation (mean value of 26% for men and 29% for women) were found in 83 pts (56%), increased serum creatinine in 44 pts (30%), cytokines activation in 133 pts (90%). CONCLUSION Our findings demonstrate that the vast majority of anemic CHF pts shows evidence of blunted endogenous erythropoietin production and/or defective iron supply for erythropoiesis. Therefore, the assessment of serum erythropoietin and the evaluation of body iron status represent a rational approach to treatment of the individual patient: according to these pathophysiologic findings in most instances, subcutaneous administration of recombinant human erythropoietin combined with iv iron would represent the optimal therapeutic approach.

Anemia Is Common in Patients With Heart Failure Seen In Specialty and Community Cardiology Clinics: Results From the STAMINA:HFP Registry (Study of Anemia in a Heart Failure Population)

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Background. Extent of anemia and factors associated with reduced hemoglobin (Hgb) in randomly selected outpatients (Pts) with heart failure (HF) have not been well described.

Methods. Anemia in HF was evaluated from the STAMINA-HFP Registry, a prospective, observational study enrolling randomly selected Pts from 12 specialty and 45 community cardiology clinics. The following characteristics were tested for their association with anemia (Hgb <12 g/dl for females; <13 g/dl for males): age, NYHA class, blood pressure, pulse, estimated glomerular filtration rate (eGFR), hypertension, diabetes, chronic obstructive lung disease, current smoking, and angiotensin converting enzyme inhibitor or beta blocker use. Anemia status was available in 982 (326 specialty; 656 community) of the 1089 Pts enrolled, who were 41% female, 75% Caucasian with an age (mean ±SD) of 64±14 years.

Results. Anemia was present in 33% and its frequency was similar in specialty and community sites (32 vs. 34%, p=0.675). Mean Hgb was 13.3±1.6 g/dl (median 13.3 g/dl). Lower eGFR, higher NYHA class, male gender, lower diastolic blood pressure, higher systolic blood pressure, and African-American ethnicity were predictors of anemia (all others p>0.15). Significant predictors of anemia are shown.

Anemia is Associated With Reduced Health Status Measures in Patients With Heart Failure: Results From the STAMINA:HFP (Study of Anemia in a Heart Failure Population) Registry


BACKGROUND Anemia is associated with adverse outcomes in heart failure (HF). However, the relationship of hemoglobin (Hgb) to quality of life (Qol) in outpatients with HF is unknown.

METHODS The association between Qol and Hgb in HF was assessed in the STAMINA-HFP Registry, a prospective, observational study enrolling randomly selected patients from HF specialty clinics involved in the UNITE-HF database or from community cardiology practice clinics. Qol was prospectively determined by telephone contact at baseline for the Kansas City Cardiomyopathy Questionnaire (KCCQ) - higher score reflects better Qol. and Minnesota Living with Heart Failure (MLHF) Questionnaire - lower score reflects better Qol. Anemia was defined as a Hgb <12 g/dl in females and <13 g/dl in males.

RESULTS Baseline Hgb, gender and Qol data were available in 780 (249 specialty, 531 community) of the 1089 patients enrolled in the registry. The cohort was 42% female, 77% Caucasian, with an age (mean±SD) of 64 ±14 years. Mean Hgb was 13.2 ± 1.8 g/dl. Significant relationships between Qol and Hgb, as a continuous variable, remained after adjusting for age, gender, race, diabetes, NYHA class and LVEF for KCCQ scores (all p<0.05) and for Physical and Summary MLHF scores (p<0.03) after adjustment for all these variables except NYHA class.

11:15 a.m.

Deranged Steroid Metabolism Independently Predicts Anemia in Chronic Heart Failure

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Background: The pathogenesis of anemia in chronic heart failure (CHF) is poorly understood. It may be secondary to abnormalities in CHF. Adrenal metabolism in CHF is characterized by the predominance of catabolic (cortisol) over anabolic (androgen) steroids.

As erythropoiesis is normally stimulated by androgens and can be depressed by chronic androgen deprivation, we hypothesized that the steroid imbalance in CHF may contribute to anemia.

Methods: We assessed the relationship between plasma hemoglobin and the cortisol/dihydroepiandrosterone ratio (CDR) in 92 male CHF patients. CDR values are transformed.

Results: Mean age of patients was 61±11 y, body mass index 26.3±4.5 kg/m², NYHA class 2.6±0.7, peak oxygen consumption(VO2) 18.1±6.0 ml/kg/m², ventilation/carbon dioxide production slope 38±13, left ventricular ejection fraction 25±11%, urate 473±139 µmol/L, cortisol 410±12 nmol/L, DHEA 13.3±9.1 nmol/L, logCDR 1.57±0.33 (range: 0.89-2.53), Cockcroft-Gault calculated glomerular filtration rate (GFRc) 111±50 ml/min. 13 patients (14%) were anemic (hemoglobin < 12 g/dl, microcytosis: 1 [8%], macrocytosis: 1 [8%]). Anemic patients were older, with lower peak VO2, lower GFRc, higher urate and higher logCDR (all p<0.001). In univariate regression analysis, determinants of hemoglobin level were age, NYHA class, blood pressure, CI = confidence interval.

Conclusion. Anemia is common in randomly selected Pts with HF and is associated with standard clinical characteristics. This high prevalence supports efforts to investigate the potential beneficial effect of correcting anemia in Pts with HF.

11:45 a.m.
Chronic Infusion of Bradykinin Preserves Vascular Endothelial NO-Mediated Function and Limits the Alteration in Left Ventricular Function During Pacing-Induced Heart Failure in Conscious Dogs

Un Jin, Daniel Tondlangu, Bijan Ghaleh, Philippe Le Corvoisier, Fanny Vincent, Thierry Baroudou, Lucien Sambin, Alain Berdeaux, Bertrand Crozatier, Luc Hittinger, INSERM, Créteil, France, INSERM, Kremlin-Bicêtre, France

It has been shown that bradykinin (BK) is involved in the beneficial effects of angiotensin-converting enzyme inhibitors on vascular endothelial and left ventricular (LV) functions in heart failure (HF). However, it is not known whether BK per se exerts a protective action on vascular and cardiac functions during the development of HF. This study examined the effects of chronic BK infusion on cardiac and vascular nitric oxide (NO)-mediated endothelial functions during pacing-induced HF in conscious dogs. Sixteen beagle dogs were chronically instrumented to measure cardiac output, LV pressure, LV wall thickness and arterial pressure. After baseline recording and examining the vasodilator responses to acetylcholine (ACh, 0.3-3 µg/kg) and nitroglycerin (NTG, 10-100 µg/kg) in the control state, dogs were randomized to receive either vehicle at a rate of either 0.9% saline or BK (1 µg/µl) through the left atrium for 3 weeks. The expression of endothelial NO synthase (eNOS) in aorta, renal and coronary arteries was measured by Western blot analysis. After 3 weeks of pacing, the BK group had a lesser degree of HF as indicated by less reduction in LV systolic pressure (+10±3 vs. +19±2 mmHg; *p<0.05), LV wall thickness (+30±18 vs. +75±29%; *p<0.05), and cardiac output (-16±5 vs -32±6%; *p<0.05). Total peripheral resistance (TPR) increased in the vehicle group (+18±10%; *p<0.05) but remained unchanged in the BK group (+1±8%). In both groups during HF, TPR response to NTG was not altered. In contrast, TPR response to ACh was blunted in the vehicle group (p<0.01) but was unchanged in the BK group. Similar trends were also observed after 5 weeks of pacing. In all examined arterial beds, eNOS protein expression decreased significantly in the vehicle group but was preserved in the BK group. Thus, in conscious dogs, chronic BK infusion limits alterations in LV function and preserves vascular endothelial NO-mediated vasodilation and thereby delays the progression of HF.

CONCLUSIONS: These data suggest that anemia is associated with reduced QoL in patients with HF. Additional studies will be required to establish if this is a cause and effect relationship.

Poster Session 1144

Basic Science Studies in Animal Models of Heart Failure

Tuesday, March 09, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1144-103

Chronic Infusion of Bradykinin Preserves Vascular Nitric Oxide-Mediated Endothelial Function and Limits the Alteration in Left Ventricular Function During Pacing-Induced Heart Failure in Conscious Dogs

Un Jin, Daniel Tondlangu, Bijan Ghaleh, Philippe Le Corvoisier, Fanny Vincent, Thierry Baroudou, Lucien Sambin, Alain Berdeaux, Bertrand Crozatier, Luc Hittinger, INSERM, Créteil, France, INSERM, Kremlin-Bicêtre, France

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Conclusions. These data suggest that anemia is associated with reduced QoL in patients with HF. Additional studies will be required to establish if this is a cause and effect relationship.