Reduced Relative Lymphocyte Count in African-Americans With Decompensated Heart Failure

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Abstract: *Background:* A reduction in relative lymphocyte count (%L) has been reported in whites with heart failure that inversely correlated with jugular venous pressure thereby implicating systemic venous hypertension with splanchnic congestion. *Objectives:* To study whether a reduced %L (<20%) occurs in African-Americans (AA) with heart failure and to address pathophysiologic mechanisms having the potential to influence lymphocyte biology and survival, we monitored patients with or without systemic venous hypertension, hypoalbuminemia, hypovitaminosis D, and secondary hyperparathyroidism. *Methods:* In 131 AA (90 men; 53 ± 12 years): 113 were hospitalized, 50 with decompensated biventricular failure (DecompHF), 24 with acute left heart failure, and 39 with heart disease, but no heart failure (HDNHF); and 18 were outpatients with compensated heart failure. At the time of admission or outpatient visit, we monitored: white blood cell count and %L; and serum albumin, 25(OH)D, and parathyroid hormone (PTH). *Results:* White blood cell count did not differ among the groups, whereas %L was reduced only in those with DecompHF (15 ± 1%; $P < 0.05$) versus 25 ± 2% with left heart failure, 29 ± 1% in HDNHF, and 28 ± 3% in compensated heart failure. Serum albumin was reduced in DecompHF (2.8 ± 0.1; $P < 0.05$), but not in any of the other groups. Reduced 25(OH)D (<30 ng/mL), in keeping with hypovitaminosis D, was found in all AA, whereas elevated serum PTH (>65 pg/mL) was found only in those with DecompHF (123 ± 22 pg/mL). *Conclusions:* A relative lymphocytopenia, together with hypoalbuminemia and elevated PTH, were found only in hospitalized AA with DecompHF. These findings implicate splanchnic congestion and the enteric loss of lymphocytes and albumin with an associated secondary hyperparathyroidism.

Key Indexing Terms: African-Americans; Decompensated heart failure; Lymphocytopenia; Hypoalbuminemia; Hypovitaminosis D; Secondary hyperparathyroidism. **[Am J Med Sci 2009;337(3):156–160.]**

The characteristic symptoms and signs that constitute the congestive heart failure (CHF) syndrome, and which appear in response to expanded intra- and extravascular volumes, have their origins rooted largely in a salt-avid state mediated by effector hormones of the renin-angiotensin-aldosterone and adrenergic nervous systems.[1,2] The pathophysiology of CHF, however, extends beyond salt and water retention to include a systemic illness whose features include an immunostimulatory state. Activated lymphocytes and monocytes produce proinflammatory chemokines and cytokines.[3–7] In hospitalized white patients with heart failure, a reduction in the relative lymphocyte count (%L) is a poor prognostic marker.[8–11] Lymphocyte survival is threatened by stress-associated elevations in plasma cortisol and catecholamines, hormones generated by an activated hypothalamic-pituitary-adrenal axis.[12–14] The putative proapoptotic role for these stress-related hormones, however, could not be confirmed when they were monitored in patients having CHF with a lymphocytopenia.[10] Huehnergarth et al[10] on the other hand, found a low lymphocyte count to be inversely associated with elevations in jugular venous pressure. This would implicate that systemic venous hypertension (SVHT) and splanchnic congestion are associated with the reduced number of circulating lymphocytes. Lymphocyte loss from injured colonic epithelial cells and/or dilated intestinal lymph channels and abnormal lymphocyte processing by the gut-associated lymphoid tissue, the body's largest lymphoid tissue, may each relate to splanchnic congestion.[15–19]

The lymphocyte count in African-Americans (AA) is usually higher than whites, which may confer a resistance to lymphocytopenia.[20] Whether a reduced %L (<20%) occurs in AA with heart failure is unknown. This was the first overall objective of this study. Our second objective was to consider potential pathophysiologic mechanisms. These included the presence or absence of: (*a*) SVHT, where splanchnic congestion and enhanced enteric loss of lymphocytes could occur[21]; (*b*) hypoalbuminemia in keeping with an enteric loss of albumin; (*c*) hypovitaminosis D, a common finding in AA with CHF[22,23] and where reduced serum 25(OH)D stores could adversely influence lymphocyte survival[24]; and (*d*) secondary hyperparathyroidism (SHPT), a common accompaniment of decompensated heart failure in AA with hypovitaminosis D, where hypoalbuminemia with reduced serum ionized calcium[22,25–28] and parathyroid hormone (PTH)-mediated lymphocyte calcium overloading may alter their behavior and survival.[29] The lymphocytopenia that accompanies chronic elevations in PTH associated with chronic renal failure is commonly associated with intracellular lymphocyte calcium overloading and altered function.[30–33]

Accordingly, 3 different groups of hospitalized AA patients were examined: those with chronic decompensated biventricular failure having SVHT, acute left heart failure (LHF) without distention of systemic veins, and heart disease without heart failure (HDNHF). Findings in these hospitalized AA were compared with ambulatory AA outpatients with compensated heart failure. At the time of admission or during an outpatient visit to the cardiology clinic, white blood cell and relative lymphocyte counts were monitored, together with serum albumin, 25(OH)D, and PTH.

METHODS

Study Population

This study, approved by the institutional review board of the University of Tennessee Health Science Center, consisted of 131 AA (90 men, 41 women; 53.3 ± 11.9 years [mean ± SD], 23–103), who over a 4-month period during 2007 were

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either admitted to the Cardiology service at the Regional Medical Center (MED) here in Memphis or followed in its outpatient Cardiology Clinic.

Decompensated Biventricular Failure. Fifty AA with heart failure, defined as echocardiographic ejection fraction (<35%), were hospitalized with symptoms and signs of decompensated biventricular failure. This included evidence of expanded intravascular volume with systemic venous distention (eg, increased jugular venous pressure), auscultatory findings of functional tricuspid and mitral regurgitation, and increased extravascular volume (eg, bilateral lower extremity edema). This group included 37 men and 13 women with a mean age of 51.7 ± 13.2 years (32–103). The etiologic origin of their heart failure was a dilated (idiopathic) cardiomyopathy in over 80% with the remainder having an ischemic cardiomyopathy with previous myocardial infarction. At the time of admission, they were being treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, furosemide, and spironolactone.

Echocardiography confirmed the dilation of the inferior vena cava without respiratory variation in diameter; it further established the presence of tricuspid regurgitation and which was graded to be of moderate to marked severity. These patients were therefore considered to have hepatic and splanchnic congestion.

To confirm the presence of splanchnic congestion in patients with decompensated biventricular failure having a plethora of the inferior vena cava, a separate echocardiographic study of portal vein pulsatility[34] was conducted in 40 consecutive men followed at the Veterans Affairs Medical Center here in Memphis. Twenty-two patients had decompensated biventricular failure (71.6 ± 10.1 years) because of an ischemic (in 8) or nonischemic (in 14) cardiomyopathy and the remaining 18 patients (66.2 ± 12.7 years) had compensated heart failure because of ischemic or nonischemic heart disease. Abnormal systolic reduction in portal vein flow velocity was seen in 92% of patients with decompensated failure (vis-à-vis 8% without CHF). In severe right heart failure with tricuspid regurgitation, the high pressure in the hepatic veins is transmitted through the sinusoids to portal vein branches causing a phasic decrease in systolic portal vein velocity. This finding confirmed our clinical impression regarding the presence of splanchnic congestion in patients with decompensated biventricular failure.

Acute Left Heart Failure. Twenty-four AA (15 men, 9 women; 56.0 ± 11.0 years, 40–85) were admitted to the MED with acute LHF and pulmonary congestion secondary to coronary artery disease, without or with ST segment elevation myocardial infarction with primary revascularization, ischemic cardiomyopathy, or hypertensive heart disease. Dilation of the inferior vena cava was found in <10% and tricuspid regurgitation was graded as trace or absent in the majority. Their outpatient medical management at the time of admission included angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta blocker, furosemide, and/or spironolactone.

Heart Disease without Heart Failure. Thirty-nine AA (25 men, 14 women; 53.8 ± 11.0 years, 23–86) were admitted to the MED without clinical evidence of heart failure. This included non-ST or ST segment elevation acute myocardial infarction with primary revascularization, acute pericarditis, evaluation of chest pain in patients with known coronary artery disease, or arrhythmia.

Compensated Heart Failure. Eighteen ambulatory outpatients (13 men, 5 women; 53.2 ± 11.5 years, 36–75) with comparable reduction in ejection fraction (<35%), who were followed in the Cardiology Continuity Clinic at the MED with minimally symptomatic, compensated failure (NYHA class I and II). These ambulatory patients were comparably treated to those with decompensated failure except dosage and route of administration would have differed between those hospitalized with decompensated failure and those with compensated failure followed as outpatients.

Exclusion Criteria

We excluded patients with chronic inflammatory disorders, infection, advanced liver disease, nephrotic syndrome, or recent surgery, or who were receiving medications that could lead to lymphocytopenia, such as corticosteroids.

White Blood Cell and Relative Lymphocyte Counts, Serum Albumin, 25(OH)D, and PTH

These variables were obtained at the time of admission using standard methodologies.

Statistical Analysis

Data were analyzed using analysis of variance. Significant differences between individual means were determined using the Bonferroni multiple comparisons test. Significance was assigned to $P < 0.05$ and values presented are expressed as mean ± SEM.

RESULTS

White Blood Cell Count and Relative Lymphocyte Count

The white blood cell (WBC) count for AA patients hospitalized with decompensated heart failure was 7.55 ± 2.04 K/mm^3 (mean ± SD). It fell within the normal reference range (4–10 K/mm^3) and did not differ from the WBC count found in AA hospitalized with either acute LHF (7.29 ± 2.14 K/mm^3) or HDNHF (6.82 ± 1.53 K/mm^3). In ambulatory patients with compensated heart failure, WBC count was 7.82 ± 2.52 K/mm^3 and it was no different from hospitalized patients.

A reduction in %L, defined as <20%, was found in patients with decompensated failure and echocardiographic evidence of splanchnic congestion and tricuspid regurgitation (15.19 ± 1.12%). As seen in Figure 1, this contrasted ($P < 0.05$) to patients with acute LHF (24.91 ± 2.05%) and those with HDNHF (29.37 ± 1.21%), where it remained within the normal reference range (20%–40%), as was the case in ambulatory patients with compensated failure (28.03 ± 3.07%). Total lymphocyte counts: decompensated, 1069 ± 76; acute LHF, 1529 ± 129; HDNHF, 1915 ± 92; and compensated, 2087 ± 519. The total lymphocyte count in AA hospitalized patients with decompensated heart failure was significantly ($P < 0.05$) reduced compared with the other hospitalized patients with either acute LHF or HDNHF and to outpatients with compensated failure.

Serum Albumin

Reduced serum albumin, defined as <3.2 g/dL, was also found at the time of admission in patients hospitalized with decompensated biventricular failure (2.8 ± 0.1 g/dL; $P < 0.05$) compared with those hospitalized with acute LHF (3.3 ± 0.1 g/dL), HDNHF (3.3 ± 0.1 g/dL), or compensated failure (3.5 ± 0.1 g/dL), where each of the latter groups fell within the normal reference range (3.2–5.5 g/dL).