Chronic anemia in heart transplant patients: prevalence, risk factors, and prognostic significance

Anemia crónica en el trasplante cardiaco: prevalencia, factores predisponentes y significado pronóstico

Guillermo C. Cursack, María G. Crespo-Leiro, María J. Paniagua-Martín, Javier Muñiz, Carmen Naya, Zulaika Grille, José A. Rodríguez, Raquel Marzoa, Eduardo Barge, Ramón Ríos, Francisco Estévez, José J. Cuenca, Alberto Juffé-Stein, Alfonso Castro-Beiras

Introduction and objectives. Data on chronic anemia following heart transplantation (HT) are scarce and contradictory. Our aims were to determine the prevalence of chronic anemia after HT, to identify predisposing factors for the condition at 12 months, and to evaluate its influence on mediumterm and long-term survival.
Methods. Retrospective analysis of patients who underwent HT between 1991 and 2005 (n=457). Chronic anemia was defined as a hemoglobin level <12 g/dL.
Results. The prevalence of post-HT chronic anemia was 75.5% at 1 month, 31% at 12 months, and 26.2% at 120 months. The condition was significantly more prevalent among women than men. Predisposing factors for chronic anemia 1 year post-HT were mild-to-moderate chronic renal failure (ie, creatinine level > 1.5 mg/dL; odds ratio [OR]=2.8; 95% confidence interval [CI], 1.5-5.0), female sex (OR=6.4; 95% CI, 3.1-13.2), and immunosuppression with mycophenolate mofetil compared with azathioprine (OR=2.6; 95% CI, 1.4-4.8). The prevalence of chronic anemia 12 months after HT was independent of the donor's sex, the recipient's age, the etiology of the recipient's heart failure, diabetes mellitus, mild-to-moderate graft rejection, cytomegalovirus infection, and angiotensin-converting enzyme inhibitor treatment. The presence of chronic anemia 12 months after HT did not influence either long-term survival (mean, 11.5 years with chronic anemia vs 13.0 years without) or actuarial survival.
Conclusions. Post-HT chronic anemia is common, but improves with time and treatment. Predisposing factors for the condition 1 year post-HT include chronic renal failure, female sex, and immunosuppression with mycophenolate mofetil. The presence of chronic anemia does not appear to influence long-term survival.

Introducción y objetivos. La información disponible sobre anemia crónica (AC) en pacientes con trasplante cardiaco (TC) es escasa y discordante. Nuestro objetivo fue estudiar la prevalencia de AC en pacientes post-TC, factores predisponentes de AC a 12 meses y su significa-do pronóstico a medio y largo plazo.
Métodos. Análisis retrospectivo de pacientes con TC entre 1991 y 2005 (n = 457). AC fue definida como hemoglobina < 12 g/dl.
Resultados. La prevalencia de AC post-TC fue del 75,5% a 1 mes, el 31% a los 12 meses y el 26,2% a los 120 meses, significativamente más prevalente en mujeres que en varones. Factores predisponentes de AC a 12 meses: insuficiencia renal crónica (IRC) leve-mode-rada (creatinina > 1,5 mg/dl) (*odds ratio* [OR] = 2,8; intervalo de confianza [IC] del 95%, 1,5-5); sexo femenino (OR = 6,4; IC del 95%, 3,1-13,2), e inmunosupresión con micofenolato mofetil (MMF) respecto a azatioprina (OR = 2,6; IC del 95%, 1,4-4,8). La prevalencia de AC 1 año tras el TC no se relacionó con el sexo del donante, la edad del receptor, la cardiopatía del receptor, la diabetes mellitus, el rechazo leve o moderado del injerto (= 3A), infección por citomegalovirus o tratamiento con inhibidores de la enzima de conversión de angiotensina. Tener AC a 1 año del TC no supuso diferencias en la supervivencia a largo plazo (tiempo de vida medio con AC, 11,5 años y sin AC, 13 años) ni en la supervivencia actuarial.
Conclusiones. La AC post-TC es un problema frecuente que mejora con el tiempo y el tratamiento. La IRC, el sexo femenino y la inmunosupresión con MMF predisponen a AC a los 12 meses del TC. Tener AC no parece influir en la supervivencia a largo plazo.

Key words: Heart transplantation; Anemia; Post-heart transplantation complications; Heart failure

Palabras clave: Trasplante cardiaco; Anemia; Complicaciones tras trasplante cardiaco; Insuficiencia cardiaca

Abbreviations: CA, chronic anemia; CRF, chronic renal failure; Hb, hemoglobin; HT, heart transplantation; MMF, mycophenolate mofetil

Introduction

Chronic anemia (CA) is a frequent complication after heart transplantation (HT) and transplantation of other solid organs, such as the kidney, liver, or lung.[1-4] Its prevalence varies and values between 0%[1] and 91.6% have been reported.[5] This enormous discrepancy in the literature may be related to differences in the hemoglobin concentrations (Hb) used to define anemia, in the timing of assessing post-HT patient evolution, in the immunosuppression regimen used, or in the management of post-HT anemia.

The etiology of post-HT anemia is not well understood, although it seems to be multifactorial[1,5,6]; suggested causes include immunosuppression (especially antiproliferative agents),[7] perioperative bleeding, reduced intestinal nutrient absorption (iron, vitamin B[12], and folic acid), renal failure with low erythropoietin levels[8] (due to cardiorenal syndrome in advanced heart failure prior to HT or the nephrotoxicity of some immunosuppressive agents, mainly calcineurin inhibitors),[9] poor response to endogenous erythropoietin, frequent blood sampling, viral infections, and treatment with angiotensin-converting enzyme inhibitors [ACE inhibitors]). Similarly, these patients often receive chronic treatment with antiplatelet agents and, occasionally, anticoagulants, which may at times favor the persistence of anemia due to occult bleeding.

According to Müller et al,[6] Hb concentrations in the first year after HT has long-term prognostic significance, although this observation has not been reproduced in other studies.[5]

Finally, there is no consensus on the treatment and prevention of post-HT anemia, which makes management of the condition different in each center and, in general, the approaches employed have been extrapolated from studies on the management of anemia in HF or in renal failure.[10,11]

The aim of this study was to improve understanding of post-HT CA, analyze the prevalence of anemia at discharge and at 1, 3, 6, 12, 24, 60, and 120 months after HT, assess predisposing factors for CA at 1 year post-HT, and determine its prognostic significance in the medium-term and long-term.

Methods

Patients

A cohort of consecutive patients with HT, admitted to Complejo Hospitalario Universitario Juan Canalejo, La Coruña between January 1991 and March 2005 (n=481). The patients were enrolled in the cohort on the day of HT, and were followed up until March 2006 or until their death, if this occurred before.

Demographic characteristics are shown in Table 1. Patients less than 16 years (n=24) were excluded.

Table 1. Demographic Data of the Patients (n=457)

Sex	
Men	383 (83.8%)
Women	74 (16.2%)
Age at HT, years	55 (10.74)
Heart disease prior to HT	
Ischemic	193 (42.2%)
Idiopathic	188 (41.1%)
Valvular	45 (9.8%)
Other	31 (6.8%)
Baseline immunosuppression	
CsA+AZA+prednisone	234 (51.2%)
CsA+MMF+prednisone	148 (32.4%)
CsA+everolimus+prednisone	9 (2%)
Other	66 (14.4%)
Creatinine concentration at 1 year, mg/dL	1.45 (0.49)
Hb at 1 year, mg/dL	12.52 (1.6)

AZA indicates azathioprine; CsA, cyclosporine; MMF, mycophenolate mofetil;
HT, heart transplantation.

Hemoglobin

Hemoglobin concentrations were collected retrospectively at different times post-HT: at discharge and at 1, 3, 6, 12, 24, 60, and 120 months after HT. Anemia was defined as Hb <12 g/dL in both men and women.[8,11] Immediately after the operation, the patients received a transfusion of concentrated red blood cells if they presented symptomatic anemia or Hb <6 g/dL.[12,13]

Other Laboratory Parameters

Chronic renal failure (CRF) was considered mild if the serum creatinine concentration was between 1.5 mg/dL and 2.49 mg/dL, moderate if the serum creatinine concentration was ≥ 2.5 mg/dL without need for dialysis or renal transplantation, and severe if the patients required dialysis or renal transplant.[9]

Prophylaxis Protocol and Treatment of Cytomegalovirus

Prophylaxis was given for 4 weeks post-HT, initially with intravenous ganciclovir and subsequently with oral valganciclovir. From this point on, patients were monitored using an antigenemia test for cytomegalovirus (CMV) and preemptive therapy given according to the protocol described.[14]

Immunosuppression

The baseline immunosuppressive regimen was changed over time. From 1991 to 2000, all the patients received induction therapy with muromonab-CD3 (OKT3) (5 mg/day; mean, 4 doses/patient).

In 2000, some patients received basiliximab (2 doses of 20 mg, days 0 and 4 post-HT), and from 2002 onwards basiliximab (and occasionally daclizumab) totally replaced OKT3.

From 1991 until April 1998, cyclosporine (CsA), azathioprine (AZA), and prednisone was used as the baseline immunosuppressive regimen. In 1995, mycophenolate mofetil (MMF) was introduced as rescue therapy instead of AZA, and in 1998 this replaced AZA as the baseline immunosuppressive regimen. In November 1997, tacrolimus was introduced in place of CsA as rescue therapy or due to the adverse effects of CsA.[15]

Acute rejection episodes (endomyocardial biopsy, ISHLT grade ≥ 3A or 2R[16]) were treated with a bolus of 250 mg to 1 g of methylprednisolone/day for 3 days. If rejection was persistent or involved hemodynamic deterioration, OKT3 or thymoglobulin was used. If antibody-mediated rejection occurred (humoral), in addition to boluses of steroids, serial plasma exchange was performed and rituximab was sometimes administered.

Other Treatment

From the immediate post-HT period until blood Hb concentrations were normalized, all the patients received prophylaxis and treatment for iron deficiency anemia using 80 mg ferrous sulfate and 350 μg folic acid (Tardyferon®). In case of suspected poor absorption of oral iron, having ruled out gastrointestinal bleeding and neoplasms, intravenous iron-sucrose (Venofer®) was administered in loading and maintenance doses. The patients with anemia and moderate CRF with normal iron concentrations (iron, 59-158 μg/dL; ferritin, 30-400 ng/dL; transferrin saturation, 20%-55%) were treated with human recombinant erythropoietin or darbepoetin alpha (Aranesp®).[7]

The patients were also treated with gastrointestinal protection agents (ranitidine or omeprazole), diuretics in case of water retention, antihypertensive agents (ACE inhibitors, angiotensin-II recipient antagonists, alpha-blocking agents, calcium channel blockers), aspirin, calcium, vitamin D, and statins (pravastatin, atorvastatin, fluvastatin, or simvastatin).

Statistical Analysis

Continuous quantitative variables were expressed as mean and standard deviation, and between-group comparisons were analyzed using the Student t test. Discrete variables were expressed as percentages, and comparisons were assessed using χ^2. Hemoglobin values were normally distributed. Conditional logistic regression models were used to asses the association between anemia and predisposing factors (donor's and recipient's age and sex, initial immunosuppressive regimen with AZA compared to MMF, diabetes

mellitus at 12 months post-HT, incidence of mild or moderate graft rejection [≥ 3A], ACE inhibitor therapy, or mild or moderate CRF). The multivariate analysis of survival-related factors was performed using Cox proportional hazard model, adjusting for clinically selected variables, such as recipient's age and sex, renal failure, and immunosuppression with AZA compared to MMF.

Statistical analysis was conducted using the SPSS for Windows statistical software package, version 14.0 (SPSS, Chicago, Ill., USA). P values <.05 were considered statistically significant. The study was conducted in compliance with laws governing the protection of personal data and in line with the international recommendations on clinical research according to the Declaration of Helsinki developed by the World Medical Association.

Results

The mean age of the 457 patients included in the study at the time of HT was 55 (10.7) years; 383 (83.8%) were men. The underlying heart condition leading to HT was ischemic heart disease in 42.2%, idiopathic dilated cardiomyopathy in 41.1%, valvular heart disease in 9.8%, and other in 6.9% (Table 1). At the time of HT, 15.3% of the recipients (n=70) were ≥ 65 years old and 32.8% had creatinine concentrations ≥ 1.5 mg/dL.

The following number of Hb values were included in the analysis: 334 at discharge, 339 at 1 month, 333 at 3 months, 326 at 6 months, 324 at 12 months, 317 at 24 months, 215 at 60 months, and 66 at 120 months.

Prevalence of Chronic Anemia

There was a high prevalence of anemia in the first months post-HT; 90.5% at hospital discharge and 75.5% 1 month after surgery (Figure 1). During the first year post-HT, the prevalence of CA gradually decreased, although more significantly in men than in women, with a statistically significant difference at 6, 12, 24, and 60 months (33.5% vs 55.2%; 24.9% vs 58.6%; 25.9% vs 49.1%; and 17.8% vs 47.1%, respectively). In the late post-HT period, the prevalence of anemia decreased to 20%-30% in men and to around 50% in women, 5 years post-HT.
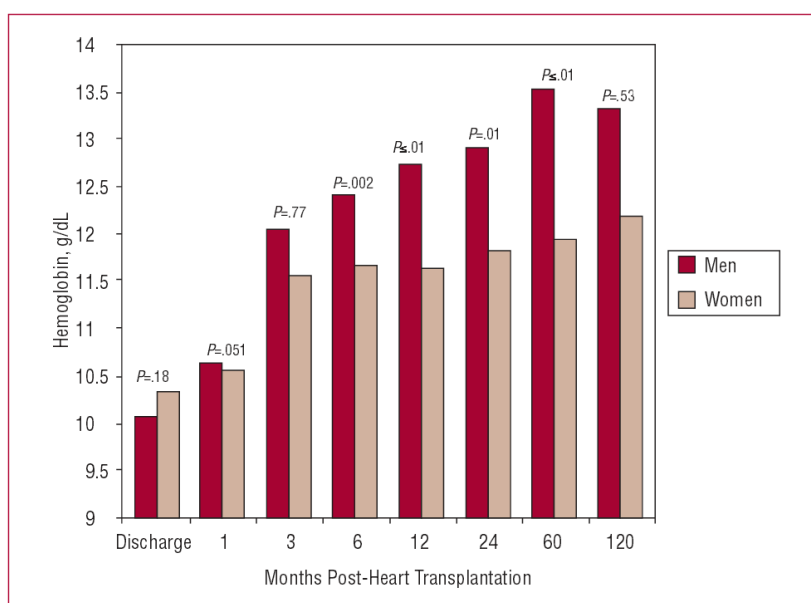

Figure 1. Mean hemoglobin concentrations after heart transplantation

Differences Between Sexes

Figure 1 shows that the Hb concentrations in women were lower than those in men from 3 months post-HT onward. This difference was statistically significant from 6 months post-HT onward.

Predisposing Factors for Anemia at 12 Months

Risk factors for CA were analyzed at 1 year, since, like other authors, we consider this sufficient time for confounding factors to balance out during the immediate postoperative period in the post-HT patient.

The following factors are associated with chronic anemia at 1 year: mild or moderate CRF (CRF was present in 53% of the patients with CA vs 35.4% without CA; P =.03); female sex (34% of women with CA vs 10.8% without CA; P <.01); recipient's age (24% of the patients ≥ 65 years with CA vs 13.9% without CA; P =.02); and baseline immunosuppression with MMF (67% of the patients with MMF and CA vs 55.2% without CA; P =.04) (Table 2).

Table 2. Predisposing Factors for Anemia at 12 Months

	Without Anemia (n=223)	Anemia (n=100)	P
Recipient's age, mean (SD), years	54.53 (10.77)	56.26 (10.62)	.18
Donor's age, mean (SD), years	35.53 (12.60)	34.3 (13.23)	.42
Female recipient	24 (10.8)	34 (34)	<.01
Female donor	55 (24.7)	25 (25)	.94
Baseline immunosuppression AZA	100 (44.8)	3 (33)	.04
Baseline immunosuppression MMF	123 (55.2)	67 (67)	.04
DM in recipient at 1 year	77 (34.5)	38 (38)	.54
Renal failure in recipient at 1 year	79 (35.4)	53 (53)	.03
Cytomegalovirus at 1 year	103 (46.4)	52 (52)	.31
History of rejection	119 (53.4)	63 (63)	.10
Heart disease in the recipient			NS
Idiopathic	96 (43)	49 (49)	
Ischemic	96 (43)	37 (37)	
Valvular	21 (9.4)	9 (9)	
Other	10 (4.5)	5 (5)	
ACEi 1 year	53 (25.5)	20 (20)	.51
Recipient's age >65 years	31 (13.9)	24 (24)	.02

AZA indicates azathioprine; DM, diabetes mellitus; ACEi inhibitors, angiotensin-converting enzyme inhibitors; MMF, mycophenolate mofetil.

The variables presented in Table 2 were included in a logistic regression analysis to confirm independent predictors of CA at 12 months post-HT. The following independent predictors were identified: mild or moderate CRF (OR=2.8; 95% confidence interval [CI], 1.5-5; P =.01); female sex (OR=6.4; 95% CI, 3.1-13.2; P ≥ .01); and baseline immunosuppression with MMF compared to AZA (OR=2.6; 95% CI, 1.4-4.8; P =.03).

The prevalence of anemia at 12 months post-HT was independent of donor's sex, recipient's age, the etiology of the recipient's heart disease, diabetes mellitus at 12 months post-HT, the incidence of mild or moderate graft rejection (≥ 3A), CMV infection in the first year post-HT, and ACE inhibitor therapy.

Survival

Mean follow-up time in our cohort was 5.2 (4) years. Mean long-term survival was 12.3 years; 11.5 years in patients with CA versus 13 years in those without CA (nonsignificant difference). Chronic anemia at 1 year post-HT was not associated with differences in long-term survival. Survival in patients with CA versus those without CA at 24, 60, and 120 months post-HT was 93% versus 94%, 84% versus 86%, and 58% versus 73%, respectively (P =.66) (Figure 2). Cox proportional hazard regression showed that there was no association between any of the risk factors mentioned and medium-term and long-term survival.
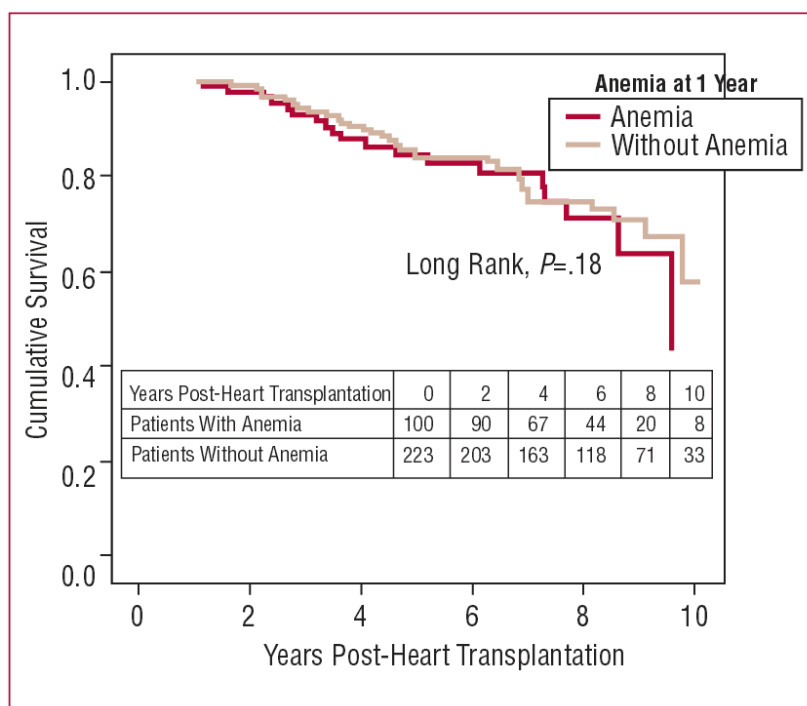
Figure 2. Kaplan-Meier curves for survival by presence of anemia 1 year post-heart transplantation.

Discussion

The general prevalence of CA in our series of 457 patients was 30% in the first year post-HT. This value was greater in women (58.6% in women vs 24.9% in men). Prevalence was very high in the first month post-HT (75.5%) and gradually decreased after replacement therapy with ferrous sulfate and folic acid. Risk factors for anemia at 1 year post-HT was female sex, renal failure or immunosuppressive regimen (MMF vs AZA).

Prevalence

The prevalence of post-HT anemia in our series differs from that reported in other series, which may be due to differences in the timing of assessing post-HT chronic anemia, and the Hb values used to define anemia. We defined anemia as Hb <12 g/dL, in line with other studies,[8,11] one of which was conducted in Spain.[11]

In 1992, Hunt et al[1] reported a prevalence of post-HT anemia of 0% at 6, 12, 18, 24, and 36 months, which is a strikingly different value from that described in current publications, although these authors defined anemia as Hb ≤ 10 g/dL, which underestimates the diagnosis of mild and moderate anemia. Their study reported that women presented lower Hb concentrations, which is in line with our results.

Müller et al[6] defined anemia as Hb <14 g/dL and reported a prevalence of 72%. They measured Hb concentrations intermittently during the first year post-HT, using the lowest value for each patient, unlike our study, in which consecutive measurements were made during the post-HT period.

In 2004, Gleissner et al[5] reported a prevalence of anemia of 91.6%, by calculating the average Hb values between 7 months and 12 months and defining anemia as Hb <14 g/dL in men and <13.5 g/dL in women. As this involved averaging the results rather than analyzing the values at different post-HT periods, their results are not comparable to ours.

Taking the foregoing into account, it is difficult to compare the different studies on prevalence of anemia in patients with HT, as well as the fact that the samples were small in these series (99 patients, Hunt et al,[1] 60, Müller et al,[6] and 156, Gleissner et al[5]).

Risk Factors and Treatment

Our finding that post-HT renal failure is a risk factor for post-HT anemia agrees with the findings of Gleissner et al[5], who also found a highly significant correlation between Hb concentrations and creatinine clearance estimated by the Cockroft-Gault formula.

Renal failure is a frequent post-HT complication with multifactorial etiology that basically includes cardiorenal anemia syndrome[17] in the patient with terminal heart failure waiting for HT, as well as post-HT renal damage (cardiopulmonary bypass and immunosuppressive regimen).

Female sex is a known risk factor for anemia in other diseases such as heart failure[18,19] ; Hunt et al[1] observed lower Hb concentrations in post-HT women.

However, female sex has never been reported as an independent risk factor for post-HT anemia. This may be due to the fact that women only form between 20% and 30% of these cohorts.

On the other hand, by adopting a single Hb value to define anemia in both women and men, the percentage of women with anemia increased in our cohort, and reached statistical significance 12 months post-HT.

It should be emphasized that female sex is also a risk factor for anemia in patients who have undergone kidney transplantation.[20,21]

Our finding that treatment with MMF versus AZA is an independent risk factor for anemia at 1 year does not agree with reports from other studies. In the only multicenter randomized study comparing MMF with AZA in HT, Eisen et al[22] and Kobashigawa et al[23] found no significant differences in Hb concentrations at 1-year follow-up or 3-year follow-up. Nevertheless, in this study only 50% of the patients continued with the assigned medication (MMF or AZA) to the end of follow-up.

Although a study comparing AZA and MMF in patients undergoing renal transplantation without graft dysfunction found that MMF was associated with greater Hb concentrations at 6 months,[24] other studies are in agreement with our finding regarding an association between MMF and anemia.[21,25]

Vanrenterghem et al[25] remarked on the unexpected association between MMF and anemia, since MMF is not known to have an antiproliferative effect on bone marrow except in lymphopoiesis.[26]

In regard to renal transplantation patients, Shah et al,[21] reported an association between graft dysfunction, change in immunosuppressive regimen to MMF, and anemia, although the real causal association would be graft dysfunction and anemia.

In a recent metaanalysis of 20 studies that included 6387 renal transplantation patients treated with MMF, Wang et al[27] did not find a statistically significant difference between subjects treated with 2 g/day or 3 g/day MMF, or any dose of AZA in the development of anemia.

Finally, our findings are based on a nonrandomized study, and thus should be confirmed by other studies.

Treatment

In the first months post-HT, iron deficiency anemia, due to bleeding and undernutrition during the perioperative period, is easily corrected with replacement therapy (oral iron and folic acid). In fact, only 31% of our patients had anemia 1 year post-HT. Other disorders have to be ruled out in these patients (such as gastrointestinal bleeding or neoplasms) and individualized treatment given. In case of iron deficiency anemia resistant to oral iron, as occurs in chronic renal failure patients not on dialysis, intravenous iron can be useful.[28]

Survival

Chronic anemia has been demonstrated as a risk factor for mortality in several cardiovascular diseases, especially in heart failure.[18,19,29-31] However, in our series, post-HT CA did not appear to influence survival, which is in line with the findings of Gleissner et al.[5] Thus, it could be said that the prognostic significance of anemia in heart failure is lost after heart transplantation; anemia remains a frequent postsurgical complication, but responds well to replacement therapy in most cases.

Limitations

Although not the aim of this study, we did not measure serum erythropoietin concentrations nor were data recorded on iron concentrations, red blood cell morphology, or bone marrow aspiration, and thus our observations regarding etiology remain merely speculative. Neither did we define anemia using different Hb values for men and women, unlike other authors.

Conclusions

Chronic anemia in HT patients is a very frequent problem in the postoperative period and at discharge, but decreases over time with appropriate treatment. Female sex, immunosuppressive regimen with MMF versus AZA, and renal failure are predisposing factors for anemia 1 year post-HT. The presence of anemia 1 year post-HT does not seem to influence long-term survival.

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