

The Effects of Pre- and Post-transplant Anemia on 1-Year Survival After Cardiac Transplantation

Anne B. Taegtmeyer, MRCP(UK), PhD,^{a,b} Paula Rogers, BSc,^a Jane B. Breen, BSc,^a Paul J. Barton, PhD,^b Nicholas R. Banner, FRCP(UK),^a and Magdi H. Yacoub, FRS^b

- Background:** Anemia is associated with a poor prognosis in heart failure. Recent studies have also suggested that anemia may be a predictor of survival after heart transplantation.
- Methods:** We investigated whether anemia before or after orthotopic cardiac transplantation affected post-transplant survival and analyzed data from a historical cohort of 267 consecutive adult patients who underwent transplantation between 1994 and 1999. Hemoglobin levels immediately before and at 6 weeks after orthotopic cardiac transplantation were recorded. Anemia was defined as a hemoglobin level less than 12 g/dl. The outcome was all-cause mortality. Survival analysis was performed using the Kaplan-Meier method and Cox proportional hazards models.
- Results:** Pre-transplant anemia was present in 26% (n = 70). One-year survival was 70% in subjects who were anemic before transplantation compared with 81% in those who were not ($p = 0.03$). Multivariate analysis showed a 1-year mortality hazard ratio for pre-transplant anemic subjects of 1.77 (95% confidence interval, 1.03–3.0, $p = 0.038$). Anemia was more prevalent after transplantation (78%). There was no difference in 1-year survival between post-transplant anemic and non-anemic subjects.
- Conclusion:** Anemia before, but not after transplantation, is a common independent predictor of 1-year survival in cardiac transplant patients. *J Heart Lung Transplant* 2008;27:394–9. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

In heart failure, anemia is associated with a poor prognosis.^{1–4} Anemia may be both a cause and consequence of chronic heart failure (CHF) and a variety of factors contribute to its development.⁵ It is presently not known, however, whether anemia affects the outcome in CHF patients who undergo cardiac transplantation.

After transplantation, anemia may be secondary to blood loss during surgery, inappropriately low erythropoietin (EPO) levels, renal impairment, bone marrow suppression secondary to drugs or viral infection, and frequent blood sampling.^{6,7} Of 45 patients studied by Müller et al,⁸ 36 (80%) were anemic within the first 6 months after transplantation. Anemia may be a predictor of survival after transplantation,^{6,8,9} and we initiated this study to investigate the effect of anemia before transplantation. We hypothesized that anemia both before and after transplantation would have an adverse

effect on outcomes. We therefore examined whether anemia, either before or after orthotopic cardiac transplantation, affected subsequent survival.

METHODS

Patients

The records of 267 consecutive adult patients who received orthotopic heart transplants between 1994 and 1999 at Royal Brompton and Harefield NHS Trust were studied retrospectively. Ethical approval for the study was granted by the Royal Brompton and Harefield Research Ethics Committee.

Subjects requiring left ventricular assist device support before transplantation were excluded from the study because of a probable higher incidence of anemia due to the preceding surgery, hemolysis, and drug side effects. No patients received EPO at any point. Follow-up data were available for all patients for at least 1 year. Most patients (90%) received immunosuppression with cyclosporine, azathioprine, and prednisolone at 6 weeks post-transplantation, according to protocol. The remaining patients were either converted to cyclosporine, mycophenolate mofetil, and prednisolone or to tacrolimus, azathioprine, and prednisolone, because of severe, resistant, or recurrent acute rejection, drug side effects, or drug interactions with the standard immunosuppression regimen. Patient and donor characteristics are reported in Table 1.¹⁰

From the ^aTransplant Unit and the ^bHeart Science Centre, Harefield Hospital, Harefield, Middlesex, United Kingdom.

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Reprint requests: Professor Sir Magdi Yacoub, Heart Science Centre, Harefield Hospital, Harefield, Middlesex, UB9 6JH, UK. Telephone: 01-895-828-893; Fax: 01-895-828-902. E-mail: m.yacoub@imperial.ac.uk

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Table 1. Patient and Donor Characteristics

| Parameter | Mean ± SD or No. (%) |
|--|----------------------|
| Recipient age, years | 47.8 ± 11 |
| Males | 223 (84) |
| Recipient weight, kg | 74.5 ± 13.9 |
| Indication for transplantation | |
| IHD | 147 (55) |
| DCM | 76 (28) |
| Congenital heart disease | 16 (6) |
| Valvular heart disease | 7 (3) |
| Other | 21 (8) |
| Pre-transplant NYHA | |
| Class III | 216 |
| Class IV | 51 |
| Pre-transplant cardiac output, Liters/min (n = 201) | 3.5 ± 1.2 |
| Pre-transplant ejection fraction, % (n = 191) ^a | 20.9 ± 10 |
| Pre-transplant serum creatinine, μmol/Liter (n = 266) | 115 ± 27 |
| Pre-transplant estimated creatinine clearance, m Liters/min ^b (n = 258) | 69.5 ± 20.4 |
| Donor age, years | 34.7 ± 12 |
| Recipient/Donor CMV serostatus-/ + (n = 233) | 41 (15) |
| Male recipient/female donor | 99 (37) |
| Ischemic time, minutes (n = 261) | 155.5 ± 60 |
| 1-year survival, % | 77.9 |

CMV, cytomegalovirus; DCM, dilated cardiomyopathy; ischemic heart disease; New York Heart Association; standard deviation.

^aMeasured by Technetium-99 multiple-gated acquisition scan (MUGA).

^bCalculated according to Cockcroft and Gault.¹⁰

Definition and Measurement of Anemia

For both men and women, a definition of anemia as a hemoglobin level of less than 12.0 g/dl was used. This definition is in keeping with that used in several studies of anemia in heart failure.¹¹⁻¹⁴ The hemoglobin level was recorded immediately before and at 6 weeks after orthotopic cardiac transplantation. Patients whose hemoglobin level immediately before transplantation was less than 12 g/dl were identified as having pre-transplant anemia. Patients whose hemoglobin level at 6 weeks post-transplantation was less than 12 g/dl were identified as having post-transplant anemia. All hemoglobin values were single measurements.

Statistical Methods

The chi-square test and unpaired Student's *t*-test were used, as appropriate. The outcome studied was all-cause mortality. The log-rank test was performed to compare survival between anemic and non-anemic patients using Kaplan-Meier survival estimates. Kaplan-Meier cumulative survival plots were constructed for display.

Univariable Cox proportional hazards analysis models were constructed using anemia and other variables known to affect post-transplant survival as covariates. Covariates were donor and recipient age, ischemic time, male recipient/female donor, recipient/donor cytomegalovirus serostatus mismatch, pre-transplant ischemic or congenital heart disease, pre-transplant New York Heart Association (NYHA) status, pre-transplant creatinine level, and pre-transplant creatinine clearance. In addition, 2 measures of pre-transplant cardiac function, left ventricular ejection fraction (measured by multiple-gated acquisition scan) and cardiac output were included. To assess whether anemia was an independent prognostic indicator, those variables that proved significant in the univariable analysis were subsequently used to construct a multivariable model. The proportional hazards assumption of the model was assessed by inspection of the log time-log hazard plot for discrete covariates.

RESULTS

Prevalence of Pre-transplant Anemia

Before transplantation, 26% patients were anemic. Of these, 52% had a normochromic normocytic anemia, 39% had a microcytosis (mean corpuscular volume [MCV] < 83 fl) and 7% a macrocytosis (MCV > 98 fl). Characteristics of the anemic and non-anemic patients are summarized in Table 2.¹⁰ Anemic patients had higher mean white blood cell and platelet counts, indicating that anemia was not secondary to global bone marrow suppression. Creatinine clearance was similar in the 2 groups.

Effect of Pre-transplant Anemia on Post-transplant Survival

One-year survival was 70% among patients who were anemic before transplantation compared with 81% for those who were not anemic (log-rank test *p* = 0.027; Figure 1). Univariable Cox analysis for 1-year survival showed pre-transplant anemia to have a hazard ratio (HR) of 1.8 (*p* = 0.03; Table 3). Other univariable predictors of death at 1 year were donor age, recipient age, ischemia time, and male recipient/female donor. A higher pre-transplant creatinine level showed a trend towards reduced survival (*p* = 0.066).

For discrete covariates, the proportional hazards assumption of the model was assessed by inspection of the log time-log hazard plot. These were parallel in all instances, indicating that the proportional hazards assumption was not violated. A multivariate Cox model was constructed using univariate predictors that gave a significance value of *p* ≤ 0.1. A final multivariable model was then constructed by serial removal of predictors that were non-significant in this multivariate model, and only pre-transplant anemia (HR, 1.77; 95%

Table 2. Characteristics of Pre-transplant Anemic and Non-anemic Patients Data are mean \pm SD or number (%), or as indicated

| Parameter | Anemic | Non-anemic | <i>p</i> -value |
|---|-----------------|-----------------|----------------------|
| Patients | 70 (26) | 197 (74) | |
| Males, % | 57 (81) | 166 (84) | 0.84 |
| Hemoglobin values, range g/dl | 8.8–11.9 | 12.0–18.2 | |
| Mean cell volume | | | |
| < 83 fl | 27 (39) | 19 (10) | <0.001 ^a |
| > 98 fl | 5 (7) | 12 (6) | NS ^a |
| White cell count $\times 10^9$ /Liter | 11.1 \pm 5.95 | 8.6 \pm 2.5 | <0.0001 ^b |
| Platelets $\times 10^9$ /Liter | 272 \pm 113 | 238 \pm 75 | 0.006 ^b |
| Creatinine, μ mol/Liter | 113 \pm 32 | 116 \pm 25 | 0.47 ^b |
| Estimated creatinine clearance, ml/min ^c | 69 \pm 22 | 70 \pm 20 | 0.86 ^b |
| Pre-transplant NYHA class | | | |
| III | 38 | 178 | <0.001 ^a |
| IV | 32 | 19 | |
| Recipient age, years | 47 \pm 11 | 48 \pm 11 | 0.51 ^b |
| Recipient BMI, kg/m ² | 24.6 | 25.3 | 0.32 |
| Donor age, years | 35.6 \pm 12.6 | 34.4 \pm 11.9 | 0.47 ^b |
| Male recipient/female donor | 25 (36) | 74 (38) | 0.79 ^a |
| Recipient/Donor CMV serostatus $-/+$ (data available for 233) | 11 (16) | 30 (15) | 0.9 ^a |
| Ischemic time, minutes | 152 \pm 55 | 157 \pm 62 | 0.59 ^b |
| Actuarial 1-year survival, % | 70 | 81 | 0.027 ^d |
| Causes of death, No. (%) | | | |
| Early graft dysfunction | 9 (43) | 10 (28) | NS ^a |
| Acute rejection | 7(33) | 8(22) | NS ^a |
| Infection | 2(9) | 8(22) | NS ^a |
| Myocardial infarction | 1(5) | 3(8) | NS ^a |
| Sudden death | 1(5) | 0 | NS ^a |
| Renal failure | 0 | 2(6) | NS ^a |
| Other | 0 | 4(11) | NS ^a |
| Unknown | 1(5) | 1(3) | NS ^a |

BMI, body mass index; CMV, cytomegalovirus; NS, not significant; NYHA, New York Heart Association

^aChi-square test.

^bUnpaired 2-sided Student's *t*-test (unequal variances).

^cCalculated according to Cockcroft and Gault.¹⁰

^dLog-rank test.

confidence interval [CI], 1.03–3; *p* = 0.039) and donor age (HR, 1.04 per year of donor age; 95% CI, 1.03–1.07; *p* < 0.0001) remained as independent predictors (Table 3).

Post-transplant Anemia

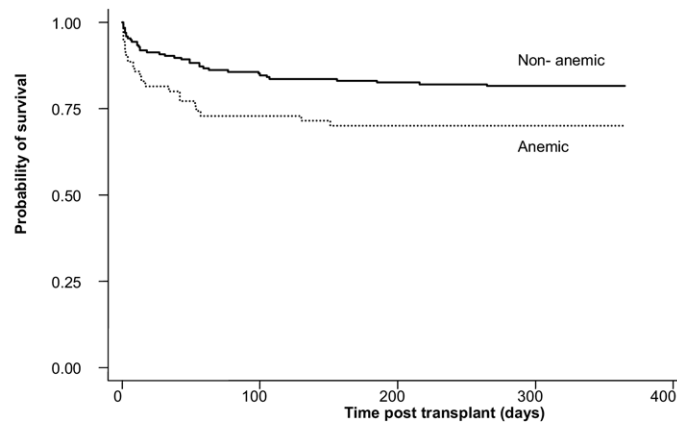
Anemia after transplantation was more common than anemia before transplantation, with 78% of the 235 patients alive at 6 weeks being anemic. Normochromic normocytic anemia accounted for 87%, microcytosis for 9%, and macrocytosis for 4%. There was no correlation between pre-transplant and post-transplant anemia (Pearson's correlation coefficient, *r* = 0.184; *p* = NS), and there was no significant difference in 1-year survival between anemic and non-anemic subjects (89% vs 87%).

DISCUSSION

Anemia is common in heart failure patients undergoing transplantation but is not traditionally considered in

pre-transplant case selection.¹⁵ We found pre-transplant anemia to be an independent predictor of death after transplantation. The prevalence of anemia increases early after heart transplantation, but post-transplant anemia was not related to death. Potential mechanisms for anemia in heart failure include associated renal impairment, side effects of drugs, hyporesponsiveness to EPO, hemodilution, and the proinflammatory state of heart failure, which causes cytokine-mediated bone marrow suppression.⁵

Microcytosis was prevalent among anaemic patients and would ordinarily prompt further investigation with iron studies. Unfortunately, insufficient data were available for a full analysis of iron status because these investigations had often been performed at a referring hospital rather than at the transplant unit; however, the median MCV among anemic patients with microcytosis was 78.4 fl (range, 69–82.7 fl), indicating that most cases had a borderline low MCV, a feature of the anemia



| Numbers at risk | | | | | |
|--------------------|-----|-----|-----|-----|-----|
| Days | 0 | 100 | 200 | 300 | 365 |
| Non-anemic at risk | 197 | 168 | 163 | 161 | 161 |
| Non-anemic events | 29 | 5 | 2 | 0 | 0 |
| Anemic at risk | 70 | 51 | 49 | 49 | 49 |
| Anemic events | 19 | 2 | 0 | 0 | 0 |

Figure 1. Kaplan-Meier plot of 1-year survival after transplantation in patients who were anemic (dotted line) or non-anemic (solid line) before transplantation. Log-rank test $p = 0.027$.

of chronic disease.¹⁶ Body mass index was calculated as an indicator of nutritional status in general and was not significantly different between the 2 groups (Table 2).

Several mechanisms could explain the link between pre-transplant anemia and post-transplant death:

1. anemia is a risk factor for cardiac surgery in general;
2. anemia may have been a marker of severity of illness before surgery, as indicated by the higher prevalence of NYHA class III and IV heart failure among anemic patients in this study (Table 1); and
3. the impact of anemia on reducing the oxygen-carrying capacity of blood, thereby increasing

Table 3. Univariable and Multivariable Cox Proportional Hazards Models for Post-transplant Survival (n = 267 Except Where Indicated)

| Predictor | Hazard ratio | 95% CI | p-value |
|--|--------------|------------|---------|
| Univariable | | | |
| Pre-transplant anemia | 1.8 | 1.06–3.1 | 0.03 |
| Donor age, years | 1.05 | 1.03–1.07 | <0.001 |
| Recipient age, years | 1.03 | 1.002–1.05 | 0.036 |
| Ischemic time, minutes (n = 261) | 1.004 | 1–1.008 | 0.053 |
| Male recipient/female donor | 1.75 | 1.04–2.95 | 0.034 |
| Pre-transplant cardiac output, Liters/min (n = 201) | 1.14 | 0.9–1.44 | 0.258 |
| Pre-transplant ejection fraction, % (measured by MUGA) (n = 191) | 1.005 | 0.97–1.04 | 0.777 |
| Pre-transplant NYHA class | 1.27 | 0.87–1.87 | 0.22 |
| Recipient CMV negative/donor CMV positive (n = 233) | 1.3 | 0.68–2.6 | 0.4 |
| Ischemic heart disease | 1.6 | 0.94–2.8 | 0.083 |
| Congenital heart disease | 1.2 | 0.44–3.36 | 0.704 |
| Pre-transplant creatinine ($\mu\text{mol/Liter}$) | 1.009 | 0.999–1.01 | 0.066 |
| Pre-transplant estimated creatinine clearance, ml/min | 0.99 | 0.98–1.002 | 0.112 |
| Multivariate | | | |
| Pre transplant anemia | 1.77 | 1.03–3.03 | 0.039 |
| Donor age, years | 1.04 | 1.03–1.07 | <0.001 |

CI, confidence interval; CMV, cytomegalovirus; MUGA, multiple-gated acquisition scan; NYHA, New York Heart Association.

cardiac work and compromising post-operative myocardial oxygen delivery.

These mechanisms may explain the observation that most deaths after transplantation occurred early (Figure 1) and were related to early graft dysfunction, which showed a trend to be more prevalent among anemic patients than among non-anemic patients (43% vs 28%, Table 2). This difference did not reach statistical significance, which may reflect a type II error.

Limitations of this study are that it is retrospective and therefore non-contemporaneous, and data were not available on the number of blood transfusions given in the peri-operative period. Owing to the variable times spent on the waiting list, it was not possible to use an average hemoglobin measure during the 4 weeks before transplantation. It was unit policy, however, to actively avoid blood transfusion in the pre-transplant period to prevent the problem of human leukocyte antigen sensitization. In end effect, this limitation will have little impact on the interpretation of the results. Furthermore, if a patient did move from the anemic to non-anemic group in such a way, this would be expected to diminish the observed effect of anemia on the post-transplant outcome.

The interesting observations regarding anemia in the peri-transplant period prompt further studies to elucidate the exact underlying mechanisms. It now remains to be determined whether pre-operative treatment of anemia improves outcome after heart transplantation. Potential treatments for pre-transplant anemia include correction of iron, folate, vitamin B₁₂ deficiency, blood transfusion, or administration of EPO. Blood transfusion for the treatment of pre-transplant anemia might be problematic because it expands intravascular volume, thereby triggering acute pulmonary edema.¹⁷ There is also a risk of sensitizing the patient against human leukocyte antigens and thus jeopardizing their chance of subsequent heart transplantation.

Studies of EPO treatment in heart failure have shown promising results,^{18,19} but data from a large multicenter trial are awaited.²⁰ Treatment with recombinant human EPO, may be associated with adverse effects, including hypertension, polycythemia, increased blood viscosity, and an increased risk of cardiovascular and cerebrovascular thrombosis.²¹ Although there were no cases of polycythemia or hypertension in the studies by Silverberg et al^{18,19} and Mancini et al,²² Besarab et al²³ found a trend towards worse survival and increased risk of non-fatal myocardial infarction in patients treated with EPO who achieved a high (> 42%) hematocrit. It remains to be shown whether treatment of anemia in CHF patients with EPO is beneficial, in particular, to those who undergo transplantation, and if so, what the optimal target hemoglobin should be.

The experience in renal transplantation, however, is in keeping with the hypothesis that treatment with EPO before cardiac transplantation may improve post-transplant outcome. A recent study by Campise et al²⁴ found hyporesponsiveness to EPO in patients awaiting renal transplantation to be a significant risk factor for death and graft failure 5 years after transplantation.

In keeping with the findings of Müller et al,⁸ post-transplant anemia was more common than pre-transplant anemia (78% at 6 weeks in the study presented here) and is largely related to intraoperative blood loss and the side effects of immunosuppressants. We did not find that anemia at 6 weeks post-transplantation was related to subsequent survival. Our data are in keeping with the previous observations of Gleissner et al⁶ in a smaller cohort of 156 transplant recipients that anemia between 7 and 12 months post-transplantation is not an independent risk factor for subsequent survival. Of 45 patients studied by Müller et al,⁸ 36 (80%) were anemic within the first 6 months after transplantation, and anemia was associated with a worse survival 3 years after transplantation (estimated survival, 82% vs 100%). A more recent study by Müller et al⁹ also showed persistent anemia during the first post-transplant year to be associated with reduced survival up to 11 years post-transplantation. Comparisons with the study presented here, however, cannot be made directly because the cohort sizes were much smaller—45 and 60 compared with 267—and different definitions of anemia and different time points were analyzed.

In patients who survive 6 weeks or more after transplantation, we found that anemia is well tolerated. This result may be due to improved cardiac function and consequent improvement in tissue perfusion.

In conclusion, pre-transplant anemia is a common and independent predictor of 1-year survival after heart transplantation. However, anemia at 6 weeks post-transplantation does not affect subsequent survival. Further studies are required to elucidate the exact mechanisms involved in this phenomenon. A randomized controlled trial in patients awaiting cardiac transplantation is needed to determine whether active treatment of pre-transplant anemia results in improved post-transplant survival.

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