Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Cardiac hepatopathy before and after heart transplantation

Wolfgang Dichtl,[1] Wolfgang Vogel,[2] Karin M. Dunst,[3] Wilhelm Grander,[1] Hannes F. Alber,[1] Matthias Frick,[1] Herwig Antretter,[3] Günther Laufer,[3] Otmar Pachinger[1] and Gerhard Pölzl[1]

1 Clinical Division of Cardiology, Innsbruck Medical University, Innsbruck, Austria
2 Clinical Division of Gastroenterology and Hepatology, Innsbruck Medical University, Innsbruck, Austria
3 Clinical Department of Cardiac Surgery, Innsbruck Medical University, Innsbruck, Austria

Keywords
cardiac cirrhosis, cholestasis, heart failure, heart transplantation, liver failure.

Correspondence
Wolfgang Dichtl MD PhD, Clinical Department of Cardiology, Innsbruck Medical University, Austria. Tel.: ++43 512 504 81307; fax: ++43 512 504 22767; e-mail: wolfgang.dichtl@uibk.ac.at

Received: 3 November 2004
Revised: 15 December 2004
Accepted: 10 February 2005

doi:10.1111/j.1432-2277.2005.00122.x

Summary

Chronic cardiac hepatopathy is a common entity in patients evaluated for heart transplantation (HTX). Hepatic injury is caused by severe heart failure resulting from prolonged recurrent congestion and/or impaired arterial perfusion. No data are available on the reversibility of cardiac hepatopathy in patients undergoing HTX. Data of 56 consecutive adult patients undergoing HTX during 2000–02 at the University Hospital of Innsbruck were analysed retrospectively. The following parameters were evaluated at the time of listing and 3, 6 and 12 months after HTX. Plasma levels of gamma-glutamyl transferase (γ-GT), alkaline phosphatase (AP), bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and total plasma protein. When listed for HTX, only 12% of all patients analysed had physiological values throughout the seven laboratory parameters assessed. Elevated levels of γ-GT, AP, bilirubin, AST, ALT, LDH and total plasma protein were detected in 66.6%, 29%, 50%, 16.7%, 10%, 40% and 18% of all patients respectively. Accordingly, median plasma levels of γ-GT, bilirubin and LDH were elevated, whereas the mean plasma level of AP was at the upper normal range. In contrast, median plasma level of AST and mean plasma levels of ALT and total plasma protein were within the normal range: γ-GT (median, 109.0; range, 634.0 U/l; $n = 36$), AP (mean, 120.2 ± 78.9 U/l; $n = 29$), bilirubin (median, 1.3; range, 16.1 mg/dl; $n = 32$), LDH (median, 226.0; range, 2355.0 U/l; $n = 33$), AST (median, 29.0; range, 145.0 U/l; $n = 36$), ALT (mean, 28.3 ± 20.8 U/l; $n = 36$) and total plasma protein (mean, 7.2 ± 1.1 g/dl; $n = 25$). Within 3 months after HTX, elevated parameters except LDH significantly ameliorated: γ-GT (median, 59.0; range, 1160.0 U/l; $P = 0.011$), AP (92.2 ± 75.2 U/l; $P = 0.016$), bilirubin (median, 0.9; range, 8.1 mg/dl; $P = 0.004$), LDH slightly increased (median, 281.0; range, 543.0 U/l; $P = 0.039$), but there was a delayed improvement of this parameter after 6 and 12 months post-HTX. End-stage heart failure is characterized by a cholestatic liver enzyme profile with elevated plasma levels of γ-GT and bilirubin. These parameters significantly improve within 3 months after HTX. Therefore, chronic cardiac hepatopathy seems to be a benign, potentially reversible disease.

Introduction

Chronic cardiac hepatopathy is a common entity in end-stage heart failure patients evaluated for heart transplantation (HTX). Hepatic injury is caused by severe heart failure resulting from recurrent congestion and/or impaired arterial perfusion. Impairment of hepatic function is frequent when right atrial pressure rises above 10 mmHg and cardiac index declines below 1.5 l/min/m^2.

The typical profile of liver function tests abnormalities in heart failure is still under debate. Elevations of transaminases as well as cholestatic enzymes or both have been reported [1–6]. Acute ischaemic liver failure, also referred to as ischaemic hepatitis or shock liver, usually manifests after an episode of severe low output status and may result in hepatocellular necrosis. Such episodes are associated with a typical increase in transaminases (up to 30 times of the upper limit of normal range) [5]. In contrast, chronic cardiac hepatopathy is characterized by elevated cholestatic parameters along with little or no changes in transaminases. Chronic liver dysfunction in heart failure is further associated with the severity of tricuspid regurgitation [6].

Histopathological patterns of liver damage in heart failure include hyperaemia (congestion of the centrolobular zone of the hepatic lobule) and collagen deposition (fibrosis) of the septa. Fibrosis severe enough to distort the normal microscopic architecture occurs in 19% of patients with chronic cardiac hepatopathy, as assessed by liver biopsy [5]. In contrast, cardiac cirrhosis continues to be a rare condition. As a result of improved heart failure treatment, cardiac hepatopathy rarely progresses to this severe stage, and/or patients die of their cardiac condition before the development of cirrhosis.

However, while successful medical treatment of heart failure may ameliorate hepatic function [7], critical evaluation of secondary organ damage is crucial when HTX is considered. No data are reported so far on the effects of HTX on cardiac hepatopathy. Hence, preoperative assessment and prediction of disease progression postoperatively is unclear. Therefore, we retrospectively analysed the characteristics and prognosis of cardiac hepatopathy in patients who underwent HTX during 2000–02 at the Medical University of Innsbruck.

Methods

Patient population

We collected data from 54 (47 male, 7 female) of 64 patients undergoing HTX in the University Hospital of Innsbruck, Austria, between 2000 and 2002. Eight patients below the age of 18 years and two adult patients with acute heart failure supported with mechanical assistance devices were excluded. Three patients receiving a re-transplantation and two patients receiving combined heart–kidney transplantation were included in the study. None of the patients had signs of chronic HBV or HCV infection. Chronic alcohol abuse was denied by all subjects. Data for appropriate analysis were available in 25–42 patients depending on the parameter assessed.

Laboratory parameters

Cut-off values for liver function tests were used according to international guidlines, taking into account the sex and age of each patient.

Statistics

Normal distribution was tested with the Kolmogorov–Smirnov test. Accordingly, nonparametric variables are expressed as median and range, normally distributed variables as mean and standard deviation. For parametric comparisons, Student's *t*-test was used. For nonparametric comparisons, Wilcoxon signed ranks test was used. Correlations were calculated by chi-squared test. A *P*-value of <0.05 was considered statistically significant. Analyses were performed using statistical software (SPSS for Windows, version 10.1, Cary, NC, USA).

Results

Cardiac hepatopathy is common in patients at listing time for HTX and is characterized by a cholestatic liver enzyme profile

As shown in Fig. 1 (left bars in each panel), cholestatic parameters are elevated in end-stage heart failure patients. When listed (Table 1) for HTX, plasma levels of γ-GT (median, 109.0; range, 634.0 U/l; $n = 36$), AP (mean, 120.2 ± 78.9 U/l; $n = 29$) and bilirubin (median, 1.3; range, 16.1 mg/dl; $n = 32$) were markedly elevated. Another increased parameter was LDH (median, 226.0; range, 2355.0 U/l; $n = 33$), as shown in Fig. 3 (left panel). In contrast, as shown in Figs 2 and 3 (right panel), plasma levels of AST (median, 29.0; range, 145.0 U/l; $n = 36$) and ALT (28.3 ± 20.8 U/l; $n = 36$) were only slightly elevated, whereas plasma levels of total protein (7.2 ± 1.1 g/dl; $n = 25$) were within normal ranges.

Elevated levels of γ-GT (cut-off limit >66 U/l in men and >39 U/l in women), AP (cut-off limit >129 U/l in men and >104 U/l in women), bilirubin (cut-off limit >1.28 mg/dl in both sexes), AST (cut-off limit >50 U/l in men and >35 U/l in women), ALT (cut-off limit >50 U/l in men and >35 U/l in women) and LDH (cut-off limit >232 U/l in men and >223 U/l in women) were noted in 66.7%, 29%, 50%, 16.7%, 9.5% and 40% of patients respectively. Decreased levels of total protein in plasma were noted in 17.9% of patients (cut-off limit <6.3 g/dl in both sexes) (Fig. 4).

Liver function tests were entirely normal in only 12% of patients ($n = 42$) (Fig. 5). One of the seven tests was pathological in one-third of patients, two tests were pathological in 19%, three in 14.3%, four in 14.3%, five

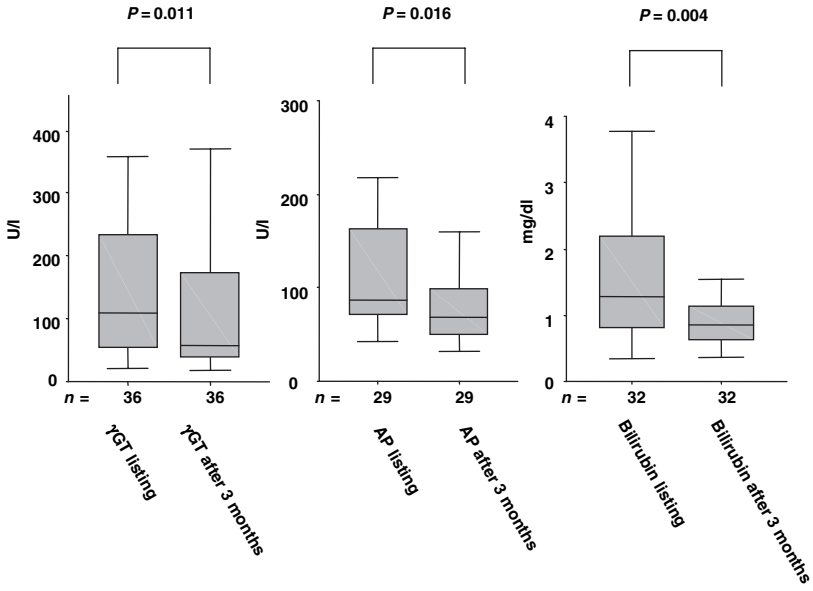

Figure 1 Bar graph illustration comparing cholestatic parameters in end-stage heart failure patients at the time of listing and 3 months after heart transplantation.

Table 1. Liver function tests the patients at listing and 3 months after HTX.

	At listing					3 months Post-transplantation				
	n	Mean	SD	Median	Range	Mean	SD	Median	Range	*P*-value
γ-GT (n.p.)	36	164.72	150.29	109.00	634.00	146.13	216.08	59.00	1160.00	**0.011**
AP (n.d.)	29	120.24	78.92	88.00	390.00	92.24	75.24	68.00	382.00	**0.016**
Bilirubin (n.p.)	32	1.95	2.78	1.28	16.09	1.18	1.40	0.86	8.06	**0.004**
AST (n.p.)	36	38.72	28.99	29.00	145.00	33.11	15.04	28.05	65.00	0.280
ALT (n.d.)	36	28.25	20.77	22.00	97.00	26.69	21.94	20.50	102.00	0.750
LDH (n.p.)	33	386.58	494.87	226.00	2355.00	319.36	126.80	281.00	543.00	**0.039**
Protein (n.d.)	25	7.24	1.05	7.00	3.00	7.10	0.68	7.20	2.56	0.740

γ-GT, gamma-glutamyl transferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; n.d., normally distributed; n.p., nonparametric.

in 4.8% and six in 2.4%. None of the patients had pathological values in all seven laboratory tests included in the study.

There were no correlations between transaminases and cholestatic parameters with mean right atrial pressure (9.7 ± 6.8 mmHg) and pulmonary artery pressure (33.4 ± 9.2 mmHg) at listing time. However, mean pulmonary pressure showed a positive correlation with severe cardiac hepatopathy as defined by the presence of two or more pathological liver function tests ($r = 0.4$; $P = 0.041$).

Reversibility of cardiac hepatopathy in patients after HTX within 3–12 months

As shown in Fig. 1 (right bars in each panel), cholestatic parameters significantly improved within 3 months after HTX: γ-GT (median, 59.0; range, 1160.0 U/l; $P = 0.011$), AP (92.2 ± 75.2 U/l; $P = 0.016$) and bilirubin (median, 0.9; range, 8.1 mg/dl; $P = 0.004$). As shown in Fig. 2 (left panel), LDH plasma levels did not ameliorate but increased within 3 months (median, 281.0; range, 543.0 U/l; $P = 0.039$). However, there was a trend to normalization of LDH plasma levels after 6 and 12 months (Fig. 4, and data not shown). There were no changes in plasma levels of AST (median, 28.1; range, 65.0; $P = 0.771$), ALT (26.7 ± 21.9 U/l; $P = 0.313$) and total protein (7.1 ± 0.7 g/dl; $P = 0.882$) levels 3 months after HTX when compared with baseline (Figs 2 and 3, right panel).

The percentages of patients with elevated levels of γ-GT decreased to 50%, 45% and 36% within 3, 6 and 12 months after HTX respectively. The percentages of patients with elevated levels of AP decreased to 18%, 7% and 12% within 3, 6 and 12 months after HTX respectively. The percentages of patients with elevated levels of bilirubin decreased to 18%, 17% and 17% within 3, 6 and 12 months after HTX respectively. The percentages of

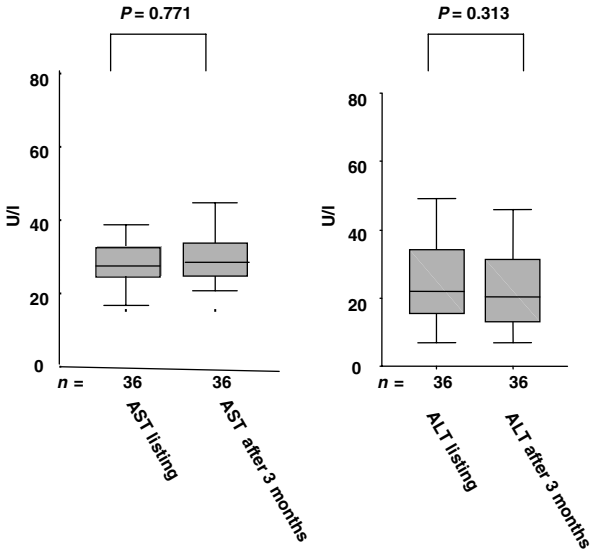

Figure 2 Comparison of hepatocellular injury-indicating enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) prior and 3 months after heart transplantation.

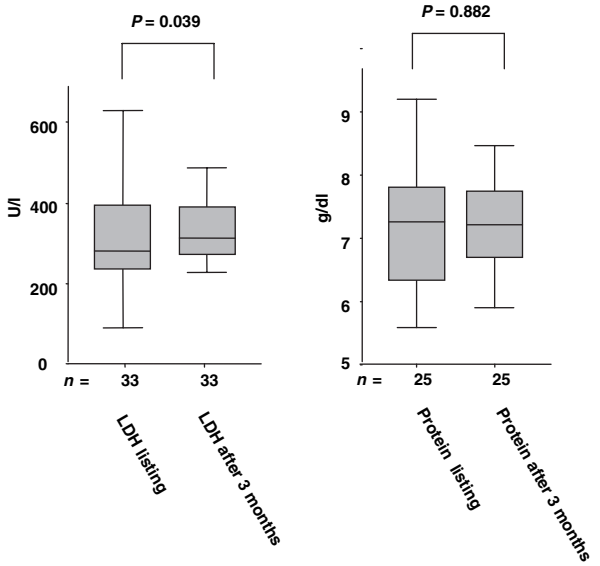

Figure 3 Graphical depiction of plasma levels of lactate dehydrogenase (LDH) and total protein compared between the time of listing and 3 months post heart transplantation.

patients with elevated levels of AST decreased to 9%, 5% and 5% within 3, 6 and 12 months after HTX respectively. The percentages of patients with elevated levels of ALT decreased to 7%, 5% and 3% within 3, 6 and 12 months after HTX respectively. The percentages of patients with elevated levels of LDH increased to 75% within 3 months postoperatively, whereas they decreased to 55% and 28% within 6 and 12 months after HTX respectively. The percentages of patients with decreased levels of total protein in plasma decreased to 11%, 0% and 0% within 3, 6 and 12 months after HTX respectively (Fig. 4).

Discussion

In this study, we show that HTX significantly improves and restores liver function within 3 months in end-stage heart failure patients suffering from chronic cardiac hepatopathy preoperatively. We also confirm recently published data suggesting that elevated cholestatic parameters (γ-GT, AP and bilirubin) rather than enzymes indicative of hepatocellular injury (AST and ALT) are the hallmark of chronic cardiac hepatopathy [4]. The improvement in cholestasis after HTX occurs despite initiation of medical immunosuppression, which may increase the risk of biliary complications [7].

The pathogenesis of cholestasis caused by chronic heart failure is poorly defined. Both local damages to the bile canaliculi because of mechanical obstruction or ischaemia as well as proinflammatory cytokine release may be involved. The cholestatic enzymes AP and γ-GT are localized to the biliary epithelium and are elevated in conditions where the bile canaliculus is damaged. Hepatic congestion may result in mechanical obstruction of bile ducts and in biliary ischaemia. This may be associated with the formation of thrombi in sinusoids, occasionally propagating to hepatic veins [8]. Increased pressure within the hepatic sinusoid because of congestion may also result in the disruption of sinusoidal endothelial cells and formation of sinusoidal to biliary fistulae, resulting from separation of the zonula occludens by increased sinusoidal pressure [6]. Inflammatory cytokines, including tumour necrosis factor-α, interleukin-1β and interleukin-6, play an important role in the pathogenesis of myocardial failure. These cytokines may also contribute to cholestasis as they inhibit expression and function of hepatobiliary transporters for bile acids and bilirubin.

Impaired liver function may be associated with an adverse prognosis after HTX. Hyperbilirubinaemia predicts clinical outcome in patients with pulmonary hypertension undergoing heart–lung transplantation [9]. Early postoperative mortality in such patients with bilirubin levels >2.1 mg/dl, between 2.0 and 1.0 mg/dl and <1 mg/dl was 58%, 27% and 16% respectively. However, although cardiac cirrhosis was found at autopsy in 75% of early deaths in patients with high bilirubin, haemolysis because of polycythemia probably adds to hyperbilirubinaemia in these patients. Hence, the results of this study cannot be transmitted to isolated heart transplant recipients without limitations. In our study, mortality was strikingly low within 2–4 years after HTX and not affected by hepatopathy

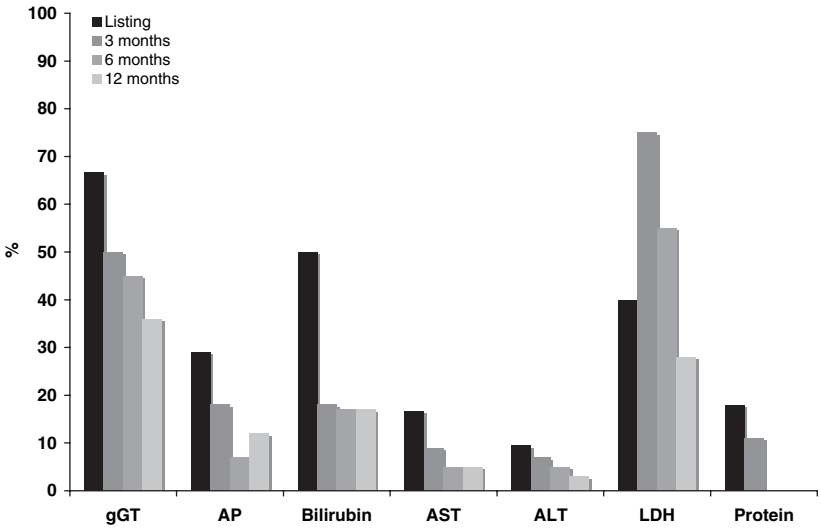

Figure 4 Bar graph illustration comparing the percentage of patients with pathological plasma levels of each liver function test at the time of listing and 3, 6 and 12 months postoperatively.

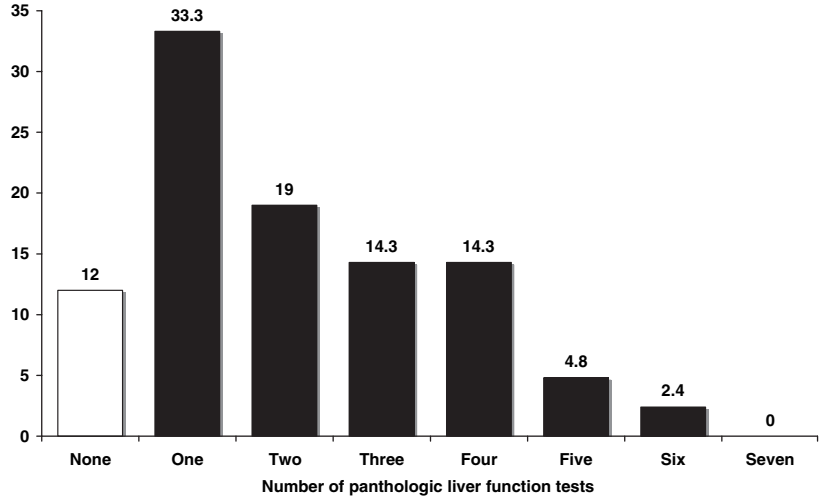

Figure 5 Graphical depiction comparing percentages of patients with pathological liver function tests at the time of listing.

before transplantation. Among the 54 patients included in our investigation, there was no perioperative mortality. One patient died during mid-term follow-up because of post-transplant lymphoproliferative disease.

In patients with long-standing cardiac cirrhosis, albumin synthesis may be impaired, with resultant hypoalbuminia, intensifying the accumulation of fluid. Although no information about albumin plasma levels was available in our patient population, total plasma protein levels were within normal ranges before and after HTX. These findings suggest that hepatic functional reserve was not affected. In addition, plasmatic coagulation was preserved. In patients receiving no anticoagulation with oral vitamin K antagonists, no changes in plasmatic coagulation parameters such as INR were detected (data not shown). In our study we could not find a correlation between liver function tests and pulmonary pressures. Hence postsinusoidal obstruction by elevated central venous pressures may only be part of the underlying mechanism in cardiac hepatopathy. Low cardiac output, hypoxemia and/or activation of inflammatory pathways might also be involved in this process.

One limitation of the study must be addressed. The data were collected in a retrospective manner. Therefore, results from only 25 to 36 of 54 patients depending on the different parameters were available. Only total bilirubin not separated into direct or indirect subforms as well as total plasma protein levels with no specific measurements of albumin were available.

In conclusion, chronic cardiac hepatopathy as characterized by elevated cholestatic parameters seems to be a benign, reversible disease and represents no contraindica-

tion to HTX. Invasive diagnostic investigations before HTX such as liver biopsy may be indicated only in patients with severely compromised hepatic function.

References

1. Batin P, Wickens M, McEntegart D, Fullwood L, Cowley AJ. The importance of abnormalities of liver function tests in predicting mortality in chronic heart failure. *Eur Heart J* 1995; **16**: 1613.
2. Sherlock S. The liver in heart failure. Relation of anatomical, functional, and circulatory changes. *Br Heart J* 1951; **13**: 273.
3. Giallourakis CC, Rosenberg PM, Friedman LS. The liver in heart failure. *Clin Liver Dis* 2002; **6**: 947.
4. Cogger VC, Fraser R, Le Couteur DG. Liver dysfunction and heart failure. *Am J Cardiol* 2003; **91**: 1399.
5. Myers RP, Cerini R, Sayegh R, *et al.* Cardiac hepatopathy: clinical, hemodynamic, and histological characteristics and correlations. *Hepatology* 2003; **37**: 393.
6. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. *Am J Cardiol* 2002; **90**: 1405.
7. Kallinowski B, Theilmann L, Zimmermann R, Gams E, Kommerell B, Stiehl A. Effective treatment of cyclosporin-induced cholestasis in heart transplantation patients treated with ursodeoxycholic acid. *Transplantation* 1991; **51**: 1128.
8. Wanless IR, Liu JJ, Butany J. Role of thrombosis in the pathogenesis of congestive hepatic fibrosis (cardiac cirrhosis). *Hepatology* 1995; **21**: 1232.
9. Kramer MR, Marshall SE, Tiroke A, Lewiston NJ, Starnes VA, Theodore J. Clinical significance of hyperbilirubinemia in patients with pulmonary hypertension undergoing heart–lung transplantation. *J Heart Lung Transplant* 1991; **10**: 317.