

Pulmonary diffusion impairment following heart transplantation: a prospective study

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ABSTRACT: The aim of this prospective study was to confirm whether and when a fall in gas transfer occurs following heart transplantation (HT); and to examine the potential relationship between gas transfer and haemodynamic change, immunosuppression, and cytomegalovirus (CMV) infection.

The lung physiology of 34 heart transplant recipients (HTR) and 14 control patients undergoing coronary artery bypass grafting (CABG) were studied. The absolute and standardized residual values of forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), residual volume (RV), forced residual volume (FRC), total lung capacity (TLC), transfer factor of the lungs for carbon monoxide (TLCO) and carbon monoxide transfer coefficient (KCO) were measured before and at 30, 60, 90, 120 and 150 days after HT. These data were compared to haemodynamic status, graft rejection, cyclosporin levels and episodes of CMV infection. Lung function was studied in a group of patients before and 4 weeks after CABG.

There was a significant fall in mean KCO after HT (pre-HT=1.29 and post-HT=1.06 mmol·min⁻¹·kPa·L⁻¹) but not after CABG (pre-CABG=1.49, post-CABG=1.5 mmol·min⁻¹·kPa·L⁻¹). No relationship was observed between gas transfer and CMV. At the latest stage following HT (150 days) there was a positive correlation between TLCO (absolute value and standardized residual) and mean cyclosporin level (r=0.48 and r=0.44, respectively) and also between the absolute KCO and actual (r=0.56) and mean (r=0.55) cyclosporin levels.

Following HT, there is an early fall in gas transfer, which is independent of the effects of surgery and bypass, implicating early immunosuppression (e.g. antithymocyte globulin/cyclosporin).

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A number of studies have suggested that abnormal pulmonary function, specifically a fall in pulmonary transfer factor, occurs following heart transplantation (HT). Several different hypotheses have been advanced as an explanation, including cyclosporin [1, 2], persistent changes associated with pulmonary venous hypertension [3], and cytomegalovirus (CMV) infection [4]. All of these studies were retrospective without control groups.

It is possible that abnormal lung function after HT reflects the effects of sternotomy and bypass. Indeed, considerable attention has been paid to the changes in pulmonary function following routine coronary artery bypass grafting (CABG) [5]. It is recognized that bypass and the resulting red cell trauma can result in the release of inflammatory mediators, which, in turn, are implicated in the aetiology of increased lung permeability following bypass [6]. In addition, a sternotomy has detrimental effects on the mechanics of lung function both by altering the mechanics of rib movement [7], and by reducing the efficiency of the thoracic muscles [8].

Other factors may influence pulmonary function, for example, heart transplant recipients (HTR) receive rabbit

antithymocyte globulin (RATG), steroids, cyclosporin and azathioprine and are, therefore, prone to routine and opportunistic infection. Preoperatively, they may have received amiodarone, and up to one third of patients awaiting transplantation are recognized as having pulmonary diffusion impairment [9], possibly resulting from chronic pulmonary congestion.

This study prospectively evaluated changes that occurred in lung function after HT in comparison to a group of patients undergoing CABG, and investigated the relationship between changes in gas transfer following transplant and rejection, cyclosporin level, human cytomegalovirus (HCMV) infection, and pulmonary capillary wedge pressure (PCWP).

Methods and patients

Patients

All patients admitted for HT to Wythenshawe Hospital from January 2, 1992 until January 7, 1993 were enrolled

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by informed consent into this study. Ethical approval was obtained from South Manchester District Health Authority Ethics Committee. There were 38 patients (34 males and 4 females; mean age 48 yrs; 20 smokers) who underwent HT during this period (ischaemic heart disease $n=25$; cardiomyopathy $n=11$; valvular heart disease $n=2$).

Four died perioperatively (graft failure $n=3$; haemorrhage $n=1$) and were not enrolled into the study. Two patients underwent no pretransplant pulmonary function tests because urgent heart transplantation was undertaken but these two patients were followed longitudinally after transplantation.

Sixteen patients undergoing routine CABG for ischaemic heart disease were enrolled as control subjects (mean age 56 yrs; 14 males and 2 females; 13 ex-smokers). All had normal left ventricular function before and after surgery as assessed clinically and by transthoracic echocardiography. One patient was excluded as a result of developing a sternal wound infection and one patient defaulted, so that 14 completed the study.

Four enrolled patients died during the study period (bowel perforation 19 days; pancreatitis 57 days; Pneumocystis pneumonia 107 days; and cholecystis/sepsis 87 days post-transplantation).

Lung function

Lung function studies were performed prior to and monthly for 6 months following HT, and before and 1 month after CABG. Twelve patients who had their first post-transplant lung function test completed before or later than 30 ± 10 days, were not included in the comparison between transplant patients and controls.

The following parameters were measured: forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), residual volume (RV), functional residual capacity (FRC), (Gould Pulmonet 111 wet spirometer); maximal inspiratory and expiratory flow volume loop; total lung capacity (TLC) (Jaeger Body Plethysmograph); single-breath transfer factor of the lungs for carbon monoxide (TL_{CO}) and gas transfer co-efficient (KCO) (PK Morgan transfer test). TL_{CO} values were corrected for haemoglobin. The definitions and methods for performing lung volumes and transfer factor followed the recommendations of the, European Coal and Steel Community [10, 11].

Cardiac function

Pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance (PVR) were collated from the preoperative assessment data. Postoperatively, PAP and PCWP were recorded at the time of right ventricular endomyocardial biopsy, taken at weekly intervals for 6 weeks and fortnightly for a further 6 weeks, and cardiac graft rejection was graded according to international classification [12].

Virology

Cytomegalovirus-specific immunoglobulin G and M (IgG and IgM) antibodies were measured by enzyme-linked immunosorbent assay (ELISA) [13]. Patients and

donors were screened for CMV-specific IgG prior to transplantation. Following transplantation, recipients were tested for CMV-specific IgG and IgM, and HCMV antigenaemia routinely at the same time as right ventricular biopsy. HCMV antigenaemia was tested for using a monoclonal antibody (mouse monoclonal antibody, Biosoft, TCS Biological Ltd, Boltolph, Claydon, Bucks, UK) against a 65 kDa lower matrix phosphoprotein (pp65) within polymorphonuclear leucocytes [14]. Prospective surveillance data using HCMV antigenaemia was available on 23 of the heart transplant recipients. All patients received acyclovir, 200 mg *t.d.s.*, as prophylaxis against herpes simplex for 3 months following transplantation. CMV hyperimmunoglobulin was given as prophylaxis to HCMV-seronegative recipients whose donors were seropositive, as detailed previously [15]. No other prophylaxis was administered to seropositive recipients during the study period.

Definitions of cytomegalovirus infection

It was considered that CMV infection was present at the time of a lung function test visit if: 1) there was current evidence of HCMV antigenaemia; 2) there was considered to be a clinical episode related to CMV (pyrexia of unknown origin, unexplained fall in white cell count) and this episode was subsequently followed by an IgM rise of greater than 4 units within 1 week of the lung function test visit; 3) there was an unexplained rise in CMV IgM (>4 units) coinciding with the lung function test visit; or 4) the IgM was raised in the presence of a clinical event considered to be related to CMV.

Immunosuppression

Immunosuppression was induced using azathioprine, $4\text{ mg}\cdot\text{kg}^{-1}$ preoperatively, and methylprednisolone 1 gram perioperatively. RATG ($1.5\text{ mg}\cdot\text{kg}^{-1}$) was given on the first three postoperative days. Maintenance immunosuppression was achieved using a triple therapy regimen of cyclosporin $5\text{ mg}\cdot\text{kg}^{-1}$ daily, azathioprine $1\text{--}2\text{ mg}\cdot\text{kg}^{-1}$ daily, and prednisolone, $0.1\text{--}0.2\text{ mg}\cdot\text{kg}^{-1}\cdot\text{daily}$.

Cyclosporin

Cyclosporin levels were routinely collected daily for the first 30 days following transplantation. Further samples were collected on each clinic visit every 2 weeks until 3 months following transplantation and then monthly until 6 months. Mean cyclosporin levels between lung function test visits and actual cyclosporin levels on the visit days were used in the analysis. Cyclosporin was measured by the enzyme multiplied immunoassay technique (EMIT) cyclosporin assay (CYVA Co., Palo Alto, CA, USA) and the dosage was adjusted to maintain the fasting whole blood concentration between $200\text{--}300\text{ }\mu\text{g}\cdot\text{L}^{-1}$.

Statistics

Pre- and postoperative absolute and standardized residuals [16, 17] for lung function were compared using

the paired Student's t-test. Standardized residual values for *KCO* were calculated from the study population *KCO* data. Pre- and postoperative haemoglobin were compared using the paired Student's t-test. A logarithmic transformation of bypass time was correlated with lung function by Pearson's correlation coefficient. Two-tailed probability and 95% confidence intervals were used. The relationship between lung function and grade of rejection, cyclosporin level, and PCWP was examined with Pearson's correlation coefficient at 30±10, 60±10, 90±10, 120±10 and 150±10 days. Nonpaired Student's t-test was used to compare the lung function of those with CMV infection to those free of infection at 60 days. The *TLCO* and *KCO* of those patients with CMV infection were compared to the *TLCO/KCO* when they were free of infection using a paired Student's t-test. All statistics were carried out on the Statistical Package for Social Services Software.

Results

Cardiac and lung function prior to transplantation (n=34)

The pretransplantation mean (and range) haemodynamic data were as follows: PAP 31 (10–48) mmHg; PCWP 24 (6–40) mmHg; cardiac output 3.2 (2.6–5.6) L; PVR 1.6 (1.1–3.4) Wood units (mmHg·min·L⁻¹); and pulmonary vascular resistance index (PVRI) 1.67 (1.6–7.1) Wood units·m⁻².

There was a negative correlation between the standardized residual value of plethysmographic TLC and both the PAP and PCWP ($r=-0.36$, $p=0.04$; and $r=-0.34$, $p=0.05$, respectively). There was no correlation with gas transfer measurements.

Lung function changes at the time of surgery (HTR versus CABG)

The results detailing changes in absolute values are summarized in table 1 and the results detailing the changes

in standardized residual values are summarized in table 2. At 30 days, both HTR and CABG patients had a significant fall in TLC and FVC, with no change in FRC or RV.

The haemoglobin (Hb) concentration fell significantly in both groups postoperatively (HTR: pre-Hb, mean 13.7 g·dL⁻¹, post-Hb, mean 11.7 g·dL⁻¹; $p=0.001$) (CABG: pre-Hb, mean 14.35 g·dL⁻¹, post-Hb, mean 12.7 g·dL⁻¹; $p=0.001$). The *TLCO*, corrected for changes in Hb, fell significantly in both groups. In addition, the HTR had a significant fall in *KCO*, ($p=0.006$), which was not seen in the CABG patients ($p=0.19$). There was no relationship between change in gas transfer and the duration of cardiopulmonary bypass in either group.

Lung function value at the late time-point (150 days) following cardiac transplantation

In the HTR there was no relationship at any time following transplantation between any lung function variable and concurrent rejection, or PCWP. The FEV₁ of the HTR improved significantly at the late time-point (150 days) following transplantation, from mean±SEM 2.6±0.12 L to 2.9±0.6 L after 150 days, $p=0.009$ (fig. 1a). The FEV₁/VC ratio also improved from 77±1.7% to 82±1.4%, $p=0.001$). However, at 150 days both the *TLCO* (fig. 1b) and *KCO* (fig. 1c) remained significantly lower than before transplantation (absolute *TLCO* from a mean of 6.7±0.4 to 5.4±0.27 mmol·min⁻¹·kPa⁻¹, $p=0.001$; absolute *KCO* from 1.4±0.1 to 1.02±0.05 mmol·min⁻¹·kPa⁻¹·L⁻¹, $p=0.0001$; standardized residual *TLCO* from a mean of -2.4±0.2 to -3.2±0.1 mmol·min⁻¹·kPa⁻¹, $p=0.001$; at 150 days post transplant). A positive correlation was seen between the standardized residual for *TLCO*, absolute *TLCO* and the mean cyclosporin level at 150 days ($r=0.48$, $p=0.03$; and $r=0.44$, $p=0.049$, respectively). In addition, a positive correlation was seen between the absolute *KCO* and the actual ($r=0.56$, $p=0.019$) and mean ($r=0.55$, $p=0.012$) cyclosporin levels at 150 days.

The number of episodes of CMV infection were small and when spread across the visits, only at Visit 2 (60

Table 1. – Change in actual lung function variables at 30 days following surgery

Lung function	Before surgery	After surgery	Degree of change	Standard error	95% CI	p-value
Heart transplant recipients (n=20)						
FEV ₁ L	2.7	2.5	-0.2	0.11	-0.4 to 0.03	0.23
FVC L	3.5	3.1	-0.4	0.13	-0.7 to -0.1	0.01
RV L	1.9	1.9	0	0.1	-0.2 to 0.2	0.68
FRC L	3.0	2.8	-0.2	0.5	-1.2 to 0.8	0.11
TLC L	5.5	5	-0.5	0.2	-0.9 to -0.1	0.02
<i>TLCO</i> mmol·min ⁻¹ ·kPa ⁻¹	6.5	5.5	-1.0	0.3	-1.6 to -0.4	0.002
<i>KCO</i> mmol·min ⁻¹ ·kPa ⁻¹ ·L ⁻¹	1.29	1.06	-0.3	0.07	-0.4 to -0.2	0.006
Control group (n=14)						
FEV ₁ L	3.2	2.5	-0.7	0.31	-1.4 to -0.03	0.0001
FVC L	3.9	3.1	-0.8	0.34	-1.5 to -0.06	0.0001
RV L	2.2	2.0	-0.2	0.12	-0.4 to 0.05	0.2
FRC L	2.8	2.7	-0.1	0.27	-0.8 to 0.6	0.85
TLC L	6.1	5.6	-0.5	0.3	-1.9 to -0.6 (-0.13)	0.02
<i>TLCO</i> mmol·min ⁻¹ ·kPa ⁻¹	9.2	7.5	-1.7	0.6	-3.0 to -0.4	0.0002
<i>KCO</i> mmol·min ⁻¹ ·kPa ⁻¹ ·L ⁻¹	1.49	1.5	0.01	0.1	-0.2 to 0.2	0.19

Mean values for lung function values are presented. FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; FRC: forced residual capacity; TLC: total lung capacity; *TLCO*: transfer factor of the lungs for carbon monoxide; *KCO*: carbon monoxide transfer coefficient; 95% CI: 95% confidence interval.

Table 2. – Change in standardized residual lung function values: at 30 days following surgery

Lung function	Before surgery	After surgery	Degree of change	Standard error	95% CI	p-value
Heart transplant recipients (n=20)						
FEV ₁ mL	-1.7	-1.9	-0.2	0.2	-0.6 to -0.1	0.231
FVC mL	-1.7	-2.4	-0.7	0.2	-1.1 to -0.3	0.005
RV mL	-0.2	-0.4	-0.2	0.3	-0.8 to 0.4	0.7
FRC mL	-0.5	-0.8	-0.3	0.2	-0.7 to 0.1	0.107
TLC mL	-1.7	-2.4	-0.7	0.3	-1.3 to -0.1	0.018
TL_{CO} mmol·min ⁻¹ ·kPa ⁻¹	-2.4	-3.2	-0.8	0.2	-1.2 to -0.4	0.002
KCO mmol·min ⁻¹ ·kPa ⁻¹ ·L ⁻¹	-1.55	-3.72	-2.18	0.72	-3.69 to -0.67	0.007
Control group (n=14)						
FEV ₁ mL	0.2	-2.9	-2.7	1.4	-6.1 to -0.1	0.006
FVC mL	-0.15	-1.7	-1.55	0.5	-2.6 to -0.5	0.0001
RV mL	0.1	-0.3	-0.4	0.3	-1.0 to 0.2	0.21
FRC mL	-0.5	-1.1	-0.6	0.5	-1.6 to 0.48	0.053
TLC mL	0.35	-1.9	-2.25	0.8	-3.9 to -0.5	0.02
TL_{CO} mmol·min ⁻¹ ·kPa ⁻¹	-0.3	-1.2	-0.9	0.6	-2.2 to 0.4	0.12
KCO mmol·min ⁻¹ ·kPa ⁻¹ ·L ⁻¹	0.63	0.05	-0.58	0.50	-1.66 to 0.50	0.26

Mean standardized residual lung function values are presented. Negative value indicates less than the predicted value. For abbreviations see legend to figure 1.

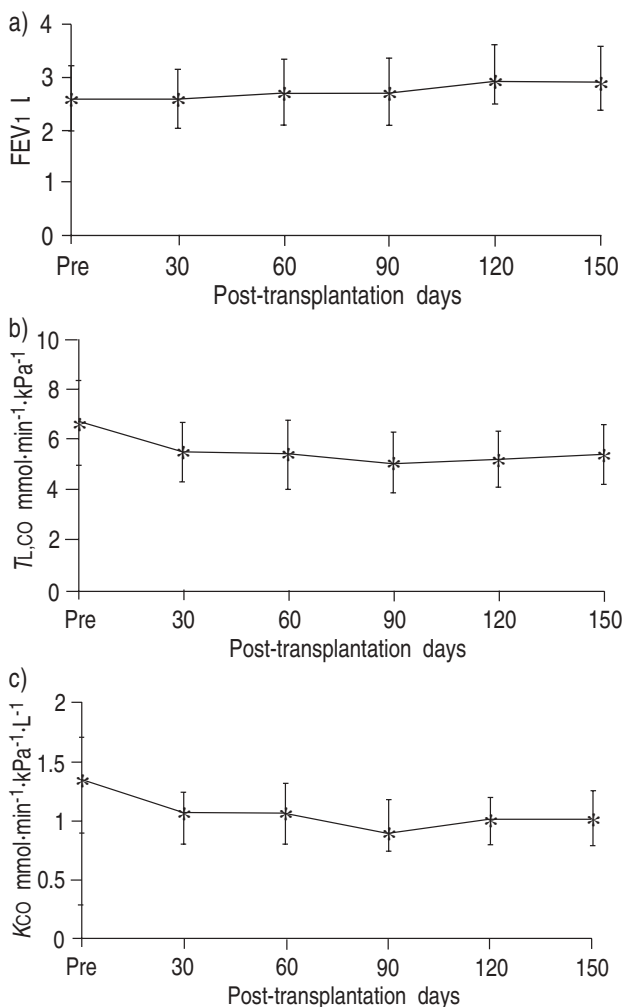


Fig. 1. – This shows the change in HTR a) forced expiratory volume in one second (FEV₁); b) transfer factor of the lungs for carbon monoxide (TL_{CO}) from before transplantation to 150 days following surgery; c) carbon monoxide transfer coefficient (KCO), from before transplantation to 150 days following surgery. Values plotted as mean \pm SD. HTR: heart transplant recipients; Pre: pretransplantation.

days) were there sufficient patients (n=6) with CMV infection at one time to allow a statistical comparison between patients with CMV infection and those free of CMV infection at that specific time-point. The presence of CMV infection was not found to influence either the standardized residual value or absolute value of TL_{CO} or KCO at 60 days following transplantation. Furthermore, no statistical difference existed between the mean TL_{CO} and the mean KCO for all the patients (n=11) who experienced CMV infection in comparison to the times when these same 11 patients were free of CMV infection.

Discussion

For this prospective study, absolute and standardized residual values for each of the lung function variables were analysed.

Standardized residual values were used in order to remove bias, which could occur by using percentage of predicted values [16, 17]. This was particularly important because the age range of the patients studied varied from 16 to 60 yrs. In older patients, relatively lower values for percentage of predicted can be expected. As the prevalence of cytomegalovirus seropositivity occurs with greater frequency in older patients, an unfair bias may have occurred in the analysis by using percentage of predicted.

The effect of cardiac failure on lung function is controversial. Lung function studies prior to transplantation were completed immediately prior to cardiac haemodynamic measurement. The only relationship observed was a negative correlation between the standardized residual value of TLC and the PAP and PCWP. This finding suggests that changes in lung volumes closely reflect the influence of treated left heart failure on the lung. The diffusion impairment observed in up to one third of patients awaiting heart transplantation [9] was also documented in this group of patients (table 2). As there was no relationship between haemodynamic status and gas transfer, these changes may result from other factors, *e.g.*

pulmonary embolism or drug toxicity [18]. Although both the FEV₁ and FVC are proportionately reduced prior to transplantation (table 2), at the late time-point following transplantation the patients had a significantly improved FEV₁, (fig. 1) and FEV₁/VC ratio. This suggests that treated left heart failure additionally has an obstructive influence on the lung. Therefore, the physiological pattern of lung function in patients with treated heart failure awaiting heart transplantation includes a diffusion/restrictive defect and an obstructive defect, of which the former is most prominent.

Changes in lung function after transplantation could have been due to the operation itself. However, when the CABG group and the HTR were compared pre- and postoperatively both the absolute and standardized residual lung function values showed similar changes, with the exception of *KCO*. At 30 days postoperatively, both groups demonstrated a fall in *TL,CO* but when this was corrected for changes in alveolar volume, only the HTR demonstrated a significant fall in *KCO*. Both groups had reduced lung volumes (*i.e.* a significant fall in TLC and FVC with no change in FRC or RV), which are consistent with chest wall changes as a result of surgery [19], emphasizing the importance of a restrictive influence by the chest wall on pulmonary physiology [20, 21].

At the early time-point following surgery (30 days) the lung volume changes observed in the HTR were not as pronounced as in the CABG patients (tables 1 and 2). This may be explained by the fact that the HTR have an enlarged heart before surgery, resulting in lower lung volumes prior to transplantation. The reduction in heart size as a result of receiving a transplant, therefore, tended to minimize the restrictive changes induced by the sternotomy.

This prospective controlled study confirms that HTR have a fall in *KCO* by Day 30, persisting to Day 150. Some of the potential causes for the fall in the transfer coefficient after HT include bypass, changes in cardiac function, CMV infection [4], early immunosuppression (*i.e.* RATG/cyclosporin) and maintenance immunosuppression, especially cyclosporin [1, 2]. Cardiopulmonary bypass might have resulted in microvascular/alveolar injury expressed as a fall in *KCO* but these changes were not seen in the CABG group nor was there any correlation between the change in *KCO* and the duration of bypass. Recent data suggest that lung injury occurring at the CABG is independent of bypass but dependent on other factors, such as stability of systemic pressure preoperatively and the requirement for blood transfusions [22].

The improvement in cardiac function following HT may influence the changes in gas transfer, with improved left atrial pressures abolishing an artificially elevated diffusion capacity prior to transplant, perhaps existing because of pulmonary vascular engorgement [23]. However, this seems unlikely for two reasons. Firstly, because of the lack of any relationship (pre- or postoperatively) between *TL,CO* and PCWP. Secondly, although the HTR experienced a fall in Hb concentration, a comparable change in Hb concentration was seen in the CABG patients. Despite the changes in Hb concentration, both groups had a significant fall in *TL,CO*, when corrected for Hb.

Evidence which points to a new process occurring within the lungs of HTR is the contrasting changes in lung

physiology following mitral valve repair. This study demonstrated a fall in gas transfer following HT and normalization of haemodynamics, whereas following mitral valve repair the lung physiology remains the same [24], or improves [25], despite persistently raised pulmonary artery pressures [24].

Events immediately following transplantation may have a role in the development of the physiological changes observed, but this study did not identify a definitive causal factor. In contrast to the control group, the induction of immunosuppression is a distinguishing characteristic of the HTR group. On the basis of the introduction of agents such as RATG, one might speculate on a possible immunological mechanism for the change in gas transfer. For instance, RATG has been shown to induce proinflammatory mediators, such as tumour necrosis factor- α (TNF- α) [26] which itself is recognized as having specific effects on endothelial cells in the lungs [27]. TNF- α has also been reported to be a potentially important mediator in the development of adult respiratory distress syndrome [28].

Alternatively, as has been suggested before [1, 2] but remains unproven, the physiological changes could be caused by cyclosporin, which is introduced at the same time as RATG. Cyclosporin can affect the microvascular structure of the kidney causing nephrotoxicity, with two histological patterns, either an arteriolaropathy with narrowing of the vascular lumen or an interstitial fibrosis [29]. One might speculate that similar changes could occur at the microvascular/alveolar interface of the lung. Indeed, isolated pulmonary diffusion impairment has also been observed in renal transplant patients receiving cyclosporin [30]. A relationship between cyclosporin and a pulmonary microvascular injury is suggested by the positive statistical correlation between cyclosporin and transfer factor at 150 days following HT. Such a positive correlation could only be explained by the presence of alveolar haemorrhage. Large numbers of haemosiderin laden macrophages in the bronchoalveolar lavage (BAL) of HTR have been observed by ourselves (unpublished data) and others [31]. However, a statistical correlation cannot be taken as proof of a direct causal effect.

Previously, in a retrospective study, we have identified CMV infection as a risk factor for reduced transfer factor following heart transplantation [4]. In this prospective study, we were unable to confirm this relationship. Most importantly, we have demonstrated a fall in *KCO* which predates the time of CMV infection. There are a number of factors in the current study which have helped to define the lack of relationship with CMV. Firstly, standardized residuals were used rather than percentage of predicted. Secondly, more sensitive techniques were used for the diagnosis of CMV infection. Thirdly, strict chronological time-points were adhered to for the analysis of the interaction of CMV infection and lung function. However, the number of CMV infection episodes was low and this might have diluted any effect.

This prospective study has demonstrated that patients awaiting heart transplantation had a dominant diffusion/restrictive defect in lung physiology. Heart transplant recipients then experienced a real fall in *KCO* and this seemed to be an early event following transplantation, implicating early immunosuppression. The diffusion

impairment was persistent at the late time-point following transplantation but a relationship between TL_{CO}/KCO and human cytomegalovirus infection was not demonstrated. A positive statistical correlation between TL_{CO}/KCO and cyclosporin at the late time-point following heart transplantation suggests that cyclosporin may produce a low-grade pulmonary microvascular injury.

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