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High prevalence of pulmonary diffusion abnormalities without interstitial changes in long-term survivors of liver transplantation

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Abstract Abnormalities in lung function are frequent findings in patients with terminal stage chronic liver disease. While spirometric parameters improve early after liver transplantation, a reduction in diffusion capacity has been reported up to 15 months after transplantation. It is unknown to what extent this disturbance in gas exchange occurs among long term survivors after liver transplantation. We assessed lung function in terms of spirometry, and gas exchange as well as pulmonary morphology by high resolution computed tomography (HRCT) in 40 patients 38 months (median, range 20–147 months) after liver transplantation. The prevalence of restrictive or obstructive changes was not different from predicted values. For the whole group of long-term survivors the carbon monoxide transfer coefficient (KCO) was reduced to 71.3 + 12.0% predicted ($P < 0.05$). HRCT revealed interstitial changes in only 2/40 (5.0%), emphysematous bullae in 2/40 (5.0%) and pleural thickening in 9/40 (22,5%). Diffusion abnormalities are prevalent in the majority of patients after liver transplantation, whereas spirometric abnormalities are absent also in the long term. The high prevalence of impaired gas exchange and the absence of interstitial lesions imply that changes in pulmonary blood vessels are the most likely cause.

Key words Pulmonary diffusion capacity · Spirometry · High resolution computer tomography · Bronchiolitis obliterans · Hepato-pulmonary syndrome

Introduction

In patients with chronic liver disease, intrapulmonary precapillary vasodilatation may cause significant right to left shunting and clinical symptoms of hypoxemia. Characteristically, in hepato-pulmonary syndrome (HPS) these alterations in lung perfusion are located in the lower lobes. HPS has been diagnosed in up to 50% of patients scheduled for orthotopic liver transplantation (OLT) [27, 29]. In consequence, diffusion capacity is reduced. This has been demonstrated in almost one half of the patients evaluated for OLT [21, 31]. Also, the prevalence of pulmonary hypertension and the associated deterioration in gas exchange is significantly higher among subjects with portal hypertension. The underlying mechanisms, and the question of whether these changes of HPS or pulmonary hypertension are reversible, are not fully understood [29, 42].

In addition to diffusion abnormalities, the impairment of lung function may be aggravated further by restrictive ventilation disorders due to ascites or hydrothorax [26] or obstructive ventilation disorders due to protease inhibitor deficiency or cystic fibrosis as underlying cause of terminal stage liver disease [12, 24].

In the early postoperative period relevant morbidity and mortality are caused by infectious and non-infectious pulmonary disease [2, 23, 36, 37]. Predominant manifestations are human cytomegalovirus (hCMV) or

fungal pneumonia, herpes simplex virus tracheobronchitis, and adult respiratory distress syndrome, atelectases, pleural effusions, or hematothorax. After the initial postoperative period, renal, biliary or hepatic pathology seems to cause more clinical problems than pulmonary disease [11]. In a more detailed study [28], however, diffusion abnormalities were detected 15 months following OLT in up to 36% of patients. Morphological alterations assessed by computer tomography (CT) were noted in the form of interstitial lesions and pleural thickening [28]. In a recent study, impaired diffusion was found to persist in 73% of patients at a median of 38 weeks after OLT [3].

No data are available regarding functional and structural pulmonary status in long-term survivors of OLT. We therefore investigated lung function and morphology in a group of 40 patients from a single centre at a median of 38 months after OLT. The specific questions to be investigated were: (1) To what extent are spirometric abnormalities and/or impairment of gas exchange prevalent after OLT in these patients? (2) Is there is an association of impaired diffusion capacity and the presence of pulmonary interstitial changes?

Materials and methods

Patients

On the occasion of their routine visits to the liver transplant clinic 40 consecutive patients gave informed consent to participate in this study. This sample represents all long-term survivors treated in the clinic during the study period. In the majority of the cases (32/40; 80,0%) transplantation was performed for end stage cirrhosis of varying etiology including alcohol related liver disease, cryptogenic and primary biliary cirrhosis. Among these were five patients with hepatocellular carcinoma, all of which were free of disease recurrence at the time of the study. One patient with hepatocellular carcinoma had received systemic chemotherapy before transplantation. One patient had a lobectomy for bronchial cancer ten years prior to transplantation and has been without disease recurrence since. Patient demographics are given in more detail in Table 1.

Despite missing serologic evidence on hCMV-status of organ donors, and incomplete hCMV status of recipients prior to transplantation, none of the patients had hCMV disease or infection at the time of the study or within the preceding six months. Within the first months following transplantation, however, hCMV infections were diagnosed in 18 patients (45,0%). One patient was hepatitis B virus surface antigen positive, and none had antibodies against hepatitis C virus at the time of transplantation. Except for four cases, a quadruple regimen was used to prevent graft rejection including anti-thymocyte globulin, azathioprine, cyclosporin A and corticosteroids. In 15 (37,5%) patients acute cellular rejection episodes were diagnosed and treated. At the time of study all patients were in stable condition without evidence of infection, rejection, or relevant drug toxicity. All were ambulatory and fully active in normal life. Informed consent was obtained from all patients. The study protocol conformed to the guidelines of the 1975 declaration of Helsinki and was approved by the Charité Ethics Committee.

Table 1 Patient demographic data

	n	[%]
Female gender	14	35.0
Male gender	26	65.0
Smoker	6	15.0
Ex-smoker	7	17.5
Non-smoker	27	67.5
Age at OLTx (ys)[a]	39	(13–62)
Age at study (ys)[a]	44	(18–65)
Time since OLTx (months)[a]	38	(20–147)
Etiology of liver disease prior to OLTx		
Cirrhosis alcoholic or cryptogenic	25	62.5
PBC	4	10.0
others	3	7.5
Budd Chiari Syndrome	3	7.5
Caroli Syndrome	1	
Crigler-Najjar Syndrome, Type II	1	
Cholangiocarcinoma	1	
Hemangioendothelioma	1	
Fulminant hepatic failure	1	

[a] Values are median and range (in parentheses)

Lung function

Spirometry and body-plethysmography were performed using a constant volume body-plethysmograph (Master Lab, Jäger, Würzburg, Germany). For final analysis the following parameters were selected: vital capacity (VC), forced vital capacity (FVC), forced exspiratory one second volume (FEV_1), the ratio FEV_1/FVC, total lung capacity (TLC), residual volume (RV), and the ratio (RV/TLC). For the measurement of diffusion parameters the breath holding technique using carbon monoxide (CO) was employed (Transferscreen, Jäger, Würzburg, Germany). For final analysis lung transfer factor for CO (TLCO) and the CO transfer coefficient (KCO) were selected. Blood gas analyses (AVL Omni, AVL Medical Instruments, Bad Homburg, Germany) were performed from arterialized capillary blood in all patients. All measurements were carried out according to the guidelines of the European Community for Steel and Coal (ECSC). For each individual values were also expressed in percent of predicted values derived from age – and sex matched healthy controls [13, 39].

Computer tomography

Lung structure was assessed by high resolution computer tomography (HR-CT, Somatom Plus, Siemens, Erlangen, Germany) in supine position and maximum inspiration. Scantime was 2 × 1 s and 2 mm slices were selected using a 526 × 526 image matrix and a window frame between –450 and 1400 Hounsfield units. When transparency diminished, a second series of scans was taken in prone position in order to differentiate true structural lesions from readily reversible changes due to hypostatic or ventilatory effects.

Images were evaluated independently by two separate investigators using a simple rating system, comparable to those used by other investigators (19, 41). Lesions were categorized according to presence or absence, location (ventro- or dorsobasal, apical, or subpleural), morphological appearance (reticular, nodular, linear, band-type, ground-glass), and to their degree on a four grade scale.

Table 2 Spirometric and body-plethysmographic findings

Variable	Observations			% predicted mean ± s.d.
	Mean ± s.d.	Median	Range	
VC [L]	4.11 ± 0.74	4.24	2.56–5.66	95.3 ± 13.0
TLC [L]	6.03 ± 1.00	6.16	3.59–7.99	97.0 ± 11.6
FVC [L]	4.19 ± 0.76	4.37	2.59–5.64	100.2 ± 12.3
FEV_1 [L]	3.57 ± 0.71	3.64	1.80–4.96	102.7 ± 16.1
FEV_1/FVC [%]	85.59 ± 9.81	85.65	42–100	
RV [L]	1.82 ± 0.57	1.69	0.97–3.28	98.8 ± 26.2
RV/TLC [%]	30.11 ± 7.05	29.50	17–44	97.7 ± 19.8
TLCO [mmol/min/kPa]	8.37 ± 1.84	8.32	5.16–12.10	85.1 ± 15.4
KCO [mmol/min/kPa/L]	1.42 ± 0.24	1.41	0.92 ± 1.83	71.7 ± 11.4*

* $P < 0.05$

In addition, evaluation included a rating as to lesions being uni – or bilateral, the presence or absence of hilar/mediastinal lymphadenopathy (> 10 mm), traction bronchiectasia, cysts, emphysema, honeycombing, pleural involvement or volume reduction.

Data analysis

All exploratory, summary, and statistical data analyses were performed using SPSS for Windows™ release 7.0. To test for significance of the differences between individual groups the *t*-test or the non-parametric Mann-Whitney-Test were applied. Dependence of items was assessed by Bartlett's Test of Sphericity using the General Linear Model and various multivariate tests were used to verify relations. Generally, these multivariate tests were supplemented by univariate tests. Thereafter, a regression model was constructed using estimated values to display type and degree of calculated interrelations. For evaluation of nominally structured items, the chi-square test was used. Analyses of covariance were performed to detect dependence of variables. For all evaluations the 0.05 level was considered significant. Unless indicated otherwise, values are mean + standard deviation, median, and range.

Results

Lung function

All data from lung function analysis were normally distributed and are shown on Table 2. For the whole group of long-term survivors after OLT, lung function was not different from predicted values, except for specific diffusion capacity KCO, which was significantly decreased ($P < 0.05$).

In detail, two patients (5.0%) exhibited restrictive abnormalities as defined by VC < 80% predicted or TLC < 80% predicted. FVC was normal in all patients, while FEV_1 or FEV_1/FVC revealed obstruction in two or three (5.0 or 7,5%) patients, as defined by an FEV_1 < 80% predicted or an FEV_1/FVC < 75%. Seven (17.5%) patients had an abnormal increase in RV (> 120% predicted) but on average, transplanted patients had normal RV values both in absolute terms and relative to TLC.

Gas exchange was impaired in 12 (30.0%) patients when a reduction in TLCO below 80% predicted was used as a cutoff. The degree of these changes was classified as mild (TLCO 60–79% predicted) in 10/12 (83,3%) and as moderate to severe (TLCO < 60% predicted) in 2/12 patients (16,7%). Impaired diffusion as monitored by KCO was observed at an even higher rate of 70,0% (28/40 patients) when KCO less than 80% predicted was considered diagnostic. Reduction in KCO was mild (KCO 60–79% predicted) in 21/28 (75.0%) and moderate to severe (KCO < 60% predicted) in 7/28 patients (25.0%). Blood gas analyses revealed no abnormalities (data not shown). For neither female nor male patients could a correlation between time after transplantation and decrease of predicted value of KCO be demonstrated (Fig. 1).

Multi- and univariate analyses of all parameters of lung function confirmed an association of VC with gender ($P < 0.001$) and age at transplantation ($P = 0.002$), TLC with gender ($P < 0.001$), FEV_1 with gender ($P < 0.001$) and age ($P = 0.014$), FEV_1/FVC with gender ($P < 0.001$), and TLCO with gender ($P = 0.005$), as found in the normal population. No association could be found with etiology of cirrhosis, rejection episodes, hCMV infection, time elapsed since OLT, and smoking status.

Lung morphology

High resolution CT demonstrated bilateral interstitial changes of either linear type and honeycombing, or honeycombing alone, in one (2,5%) patient each, which were classified as grade 3 in both cases; they were located in the dorsobasal lobes (Fig. 2). Other findings included emphysematous bullae in one (2.5%) patient, pleural thickening in nine (22.5%) and mediastinal or hilar lymphadenopathy in two (5,0%) patients. By visual assessment no alteration in lung volume could be detected.

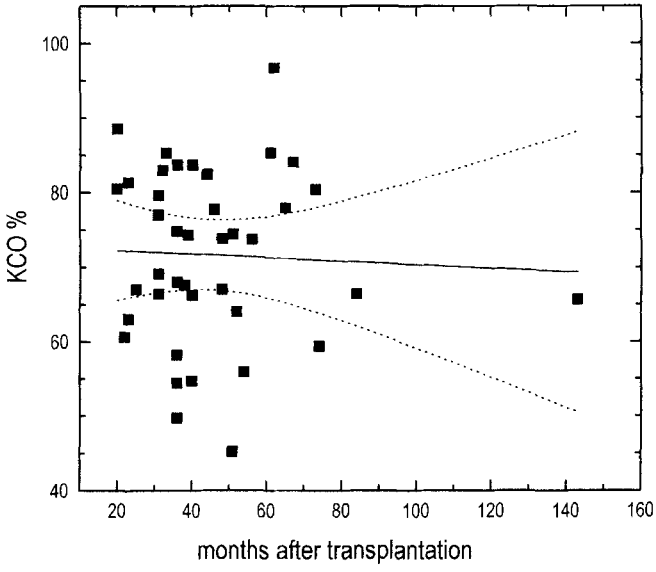


Fig. 1 Scattergraph of specific diffusion capacity (KCO), given a % predicted value, and time elapsed since liver transplantation

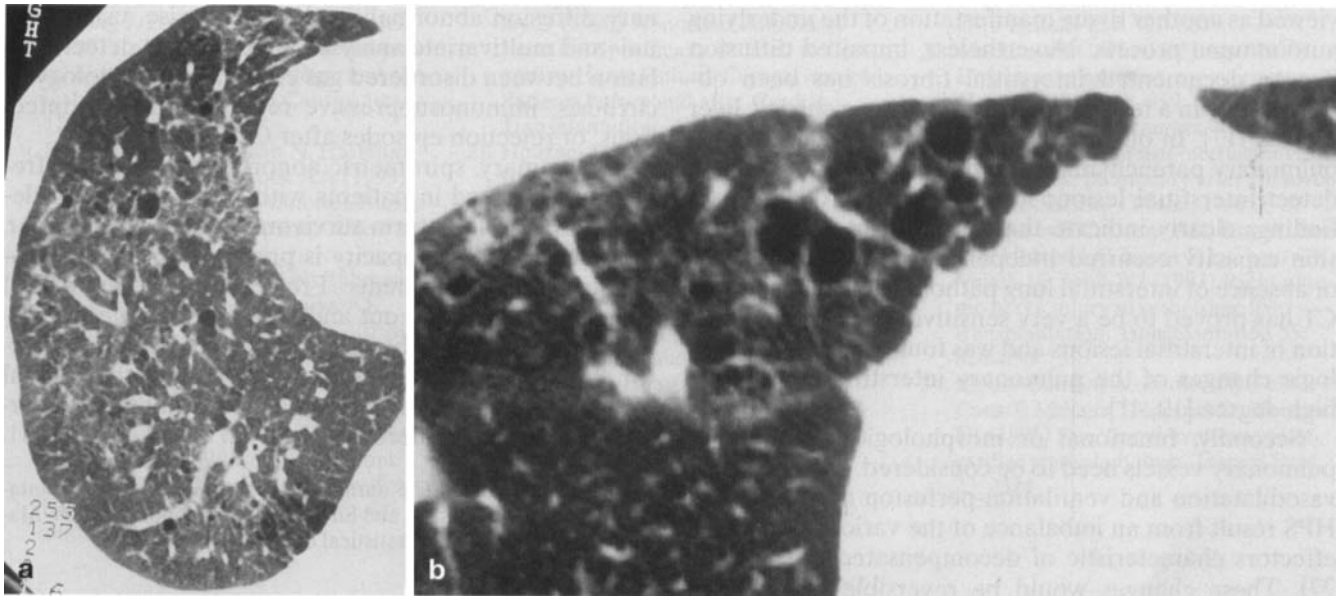
Discussion

In this group of long-term survivors of OLT the prevalence of restrictive or obstructive ventilatory disorders seems to be equivalent to that of the general population. In patients prior to OLT, however, such findings are frequent and may be reversed by paracentesis or diuretic treatment [1, 5]. Most likely, lung function improves as a consequence of successful OLT. Indeed, restrictive changes have been shown to regress within the first months after OLT [28]. This phenomenon has been observed even in children with structural pulmonary changes after OLT for cystic fibrosis [30] or alpha-1-antitrypsin deficiency [16]. Our data from long-term survivors eliminate potential confounding variables of the postoperative period, such as impaired motility of the right hemidiaphragm [33] or pleural effusions [23, 28, 37]. Despite a similar prevalence of pleural thickening and interstitial changes in our and other series [28], these abnormalities were not associated with an impairment of ventilation in long-term survivors after OLT. Pulmonary calcifications as another potential cause of restriction [23, 35] could not be demonstrated in any of our patients.

In patients with liver cirrhosis, restrictive or obstructive ventilation disorders are reversible to a major degree, following treatment of ascites with diuretics, paracentesis or after OLT. Most likely, effective therapy of ascites will relieve abdominal tension, and may thus improve ventilation mechanics. As an additional factor, after OLT the correction of pathologic body composition would result in a normalisation of the previously expanded extracellular water space [38], resulting in an increase in pulmonary compliance and improved ventilation.

From our data we cannot give an explanation for the observed association between FEV_1/FVC and gender; there was no association with smoking status as a potential cause for the observed gender association. Smoking, however, may play a role regarding the increase in RV or its proportion of TLC as observed in seven patients, two of which were smokers. As regards mean values, there was no difference between smokers or non-smokers

Fig. 2 CT scan showing interstitial changes of the linear type in the left dorsobasal region (**a**) with close up (**b**)



(data not shown). In particular, we could not demonstrate an association between cigarette smoking and impaired diffusion capacity, which is in good agreement with a recent study [3]. In summary, it may be concluded from these observations that restrictive or obstructive ventilation abnormalities appear to be fully reversible in long-term survivors after OLT. Moreover, type and degree of ventilation abnormalities prior to OLT do not seem to correlate with the occurrence of postoperative pulmonary complications [23, 31]. Therefore, patients should not be deferred from OLT because of restrictive or obstructive disorders per se.

While parameters of ventilation are normal, as discussed above, the prevalence of diffusion abnormalities approached almost 70% even after a median survival of 39 months after OLT. This is a surprising finding, since previous studies demonstrated a decrease in the prevalence of impaired diffusion from 73% at 38 weeks [3] to 36% at 15 months after OLT [28]. Several mechanisms may be involved in the occurrence of these phenomena. Obviously, disturbances in gas exchange are not readily reversible, since neither paracentesis nor diuretics for the treatment of ascites were able to improve diffusion capacity in patients with cirrhosis [1, 30]. In fact, diffusion capacity worsened in one study, and this was attributed to an increased ventilation perfusion mismatch secondary to improved ventilation of the lower lobes after paracentesis [6]. After OLT, however, the disorder in gas exchange appears to be reduced, compared to findings in patients with liver cirrhosis with ascites.

Structural lesions of the pulmonary interstitium have been discussed in patients with systemic diseases, such as cystic fibrosis, protease inhibitor deficiency, or Sjögren's syndrome [17]. Similarly, pulmonary changes in patients with primary biliary cirrhosis [24] have been viewed as another tissue manifestation of the underlying autoimmune process. Nevertheless, impaired diffusion due to documented interstitial fibrosis has been observed only in a few cases of terminal stage chronic liver disease [17]. In our series, morphological evaluation of pulmonary parenchyma by high resolution CT failed to detect interstitial lesions in patients after OLT. These findings clearly indicate that impairment of the diffusion capacity occurred independently of the presence or absence of interstitial lung pathology. High resolution CT has proved to be a very sensitive tool for the detection of interstitial lesions and was found to predict histologic changes of the pulmonary interstitium to a very high degree [19, 41].

Secondly, functional or morphological changes of pulmonary vessels need to be considered. Inappropriate vasodilatation and ventilation-perfusion mismatches of HPS result from an imbalance of the various vasoactive effectors characteristic of decompensated cirrhosis [7, 27]. These changes would be reversible by OLT. In hemodynamic terms, both the regression to normal and the persistence of relevant right to left shunting have been described [29].

Structural abnormalities of the pulmonary vasculature are prevalent in patients with liver disease [8, 44] and their persistence after OLT may be related to the observed prevalence of impaired gas exchange in grafted patients. In cirrhotic patients without pulmonary hypertension extensive alterations of pulmonary vessels have been demonstrated [32]. At present, our knowledge of the precise factors involved in the pathogenesis and reversibility of pulmonary vascular changes is incomplete [25]. Morphological evidence as to the question of vascular remodelling is lacking.

Therefore, in the absence of interstitial lung disease and of spirometric and body-plethysmographic abnormalities, we consider changes in the pulmonary blood vessels as the most likely cause for the observed impairment in gas exchange. This view is supported by the fact that all measurements have been corrected for blood hemoglobin concentration and no patient had hypoxemia indicative of HPS.

In good agreement with this hypothesis, persisting abnormalities in the diffusion capacity and the resolution of restrictive and obstructive changes have been observed following successful heart transplantation [4, 18, 20, 40]. This has been attributed to a thickening of the alveolo-capillary membrane [9, 40, 45]. Recently, we could confirm these findings in 642 patients followed up to 11 years after heart transplantation [15]. Concering potential causes hCMV infection and/or immunosuppressive drugs, such as cyclosporin A controversial findings exist [18, 22, 34, 43]. In our patients after heart transplantation we were unable to demonstrate that different immunosuppressive regimens or hCMV infection were significantly correlated to the presence of pulmonary diffusion abnormalities [14]. Likewise, using both uni- and multivariate analyses, we could not detect a relation between disordered gas exchange and etiology of cirrhosis, immunosuppressive regimens, hCMV infections, or rejection episodes after OLT.

In summary, spirometric abnormalities that are frequently observed in patients with cirrhosis are not demonstrable in long-term survivors after OLT. However, impaired diffusion capacity is prevalent in a large proportion of these patients. From our data, interstitial changes can be ruled out and therefore changes in pulmonary vessels may be an important pathogenetic factor. The precise mechanisms involved and the clinical relevance of abnormal gas exchange are not fully understood and need further investigation.

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