

# Pulmonary hypertension and lung transplantation: *Thorax* publication activity review 2008–2010

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## ABSTRACT

A review is presented on articles published in *Thorax* between 2008 and 2010 relating to lung transplantation and pulmonary hypertension.

## PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a rare condition that causes a significant reduction in pulmonary blood flow and a low cardiac output state. It is associated with a poor prognosis due to development of progressive right heart failure secondary to increased pulmonary vascular resistance (PVR). PH is defined physiologically by a mean pulmonary arterial pressure (mPAP)  $\geq 25$  mm Hg at rest or  $\geq 30$  mm Hg during exercise in the presence of a non-elevated pulmonary wedge pressure  $\leq 15$  mm Hg and PVR  $\geq 3$  Wood units. Although rare, the incidence of PH is increasing, perhaps due to better recognition of the disease, and the prevalence has been estimated to be up to 15 cases per million population.<sup>1</sup> It is essential that an accurate diagnosis is made promptly, as patients derive symptomatic and prognostic benefits from the increasing armoury of targeted treatments. Patients who do not have treatment have a life expectancy of  $< 3$  years.<sup>2</sup>

Over the past 2 years, three original articles that have examined various aspects of PH have been published in *Thorax*.

## Understanding the pathophysiology of PAH

Idiopathic pulmonary arterial hypertension (iPAH) in children shows certain similarities in pathophysiology to adult iPAH, with vascular changes of medial hypertrophy, neointimal proliferation and plexiform lesions, as well as similar patterns of disturbed vascular and endothelial function.<sup>3,4</sup>

The paper by Hall *et al*<sup>5</sup> used immunohistochemistry to compare the distribution, characterisation and number of inflammatory cells in periarterial infiltrates from the lungs of 9 healthy children, 15 children with iPAH and 9 children with pulmonary arterial hypertension associated with congenital heart disease. Additionally, the structural differences in lung vasculature between patients with iPAH treated with intravenous prostacyclin and an endothelin receptor antagonist and those untreated were compared to determine if there was evidence of reversal of vascular remodelling with use of targeted treatments.

The authors reported the presence of extensive periarterial infiltrates made up of macrophages and T lymphocytes. In addition there was increased cellular staining for S100A4, a calcium-binding

protein which regulates cellular processes such as proliferation and migration, and of bone morphogenetic protein receptor type-2 (BMPR2)-positive cells in the lung peripheries of patients with iPAH that were not present in the other cohorts. Patients who were treated with prostacyclin and endothelin receptor blockade did not demonstrate any structural remodelling of the pulmonary vasculature. However, they did show significant reduction in endothelial cell activation as evidenced by positivity for human leucocyte antigen (HLA)-DR expression (treated group 17%, untreated group 100%,  $p < 0.002$ ).

Although correlation does not equate to causation, and paediatric iPAH may ultimately prove to have a different underlying mechanisms to adult iPAH, this study offers potential new insights into the pathophysiology of iPAH. It supports the concept of a multiple hit hypothesis and a role for inflammation in paediatric iPAH, where an underlying genetic predisposition to pulmonary vascular disease is activated by a second hit such as infection.<sup>6,7</sup> The observations suggest there may be some merit in investigation of anti-inflammatory approaches in iPAH to help ameliorate the high morbidity and mortality rates of these patients.

## Morbidity in patients with PAH

Patients with iPAH can experience significant impairment to their quality of life. This includes a reduced exercise tolerance as evidenced by a decline in their 6 min walk distance (6MWD) and symptoms of dyspnoea and lethargy. These can cause marked limitations in activities of daily living that often persist despite targeted treatment.<sup>8</sup> The poor functional status of many patients has been attributed to persistent cardiac and respiratory impairment<sup>9</sup>; however, Mainguy and colleagues in Quebec<sup>10</sup> hypothesised that peripheral muscle function may be abnormal in these patients. In their study they assessed peripheral muscle function, fibre morphology and the enzymatic profile of patients in order to assess peripheral muscle dysfunction.

Ten patients with WHO functional class II or III due to iPAH were compared with 10 matched controls. It was shown that those with iPAH had lower numbers of type 1 muscle fibres ( $p = 0.05$ ), lower maximal voluntary contraction ( $p = 0.05$ ), lower potentiated quadriceps twitch ( $p = 0.01$ ) and reduced quadriceps strength ( $p = 0.05$ ). Furthermore, enzymatic analysis revealed an increased muscular phosphofructokinase/3-hydroxyacyl-CoA-dehydrogenase ratio ( $p = 0.05$ ), indicative of a higher potential for anaerobic metabolism in patients with iPAH.

The results are in keeping with previous findings of peripheral muscular dysfunction in other chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD)<sup>11</sup> and idiopathic pulmonary fibrosis (PF).<sup>12</sup> This lends credence to the concept of approaching these conditions as lung diseases with systemic manifestations. It also suggests that chronic respiratory diseases may have a similar systemic effect, regardless of their aetiology. Whether this is a process that is driven by inflammation, as alluded to in the paper by Hall *et al* above, remains a matter for further research.

Although the search for the underlying mechanism of peripheral muscle dysfunction may lead to novel muscle-targeted therapies in the future, it does indicate that there might be a role for a rehabilitation programme in improving patients' morbidity. This was looked into by the same team in Quebec<sup>13</sup>; in a recent pilot study, they demonstrated that a 12-week rehabilitation programme led to improvements in 6MWD in a group of five patients with iPAH. A separate study<sup>14</sup> did not demonstrate an improvement in 6MWD, but showed significantly improved endurance capacity and quadriceps strength after training. A more comprehensive prospective trial would be needed, but the results do serve to remind us that while we persevere with expensive targeted medicines in the treatment of iPAH to improve survival, there might be scope to reduce morbidity with the implementation of relatively simpler forms of interventions such as exercise rehabilitation.

### Mortality in patients with secondary PH

Even in the 21st century, PH remains a progressive and ultimately life-threatening disease with no cure. Although advances over the past two decades have led to improving survival rates,<sup>15</sup> there remains a need to identify patients who are at increased risk of deterioration as well as those who have a better prognosis.

One of the complicating factors in determining prognosis in PH is the diverse range of underlying conditions that are associated with the development of PH. For example, the prognosis for patients with PH associated with systemic sclerosis is worse than that for patients with iPAH.<sup>16</sup> Prognostic markers also differ between different aetiologies of PH. Idiopathic, familial and anorexigen-associated PH have increased mortality closely associated with male gender, right ventricular dysfunction and exercise limitation,<sup>17</sup> whereas raised right atria pressures were the strongest haemodynamic predictor of mortality in PH associated with systemic sclerosis.

However, little is known about the prognostic relevance of different haemodynamic variables in PH secondary to established intrinsic lung disease. Corte *et al*<sup>18</sup> compared PVR, mPAP and other haemodynamic variables from right heart catheterisation in 66 patients with severe diffuse interstitial lung disease to evaluate their prognostic value. In addition, they assessed the prognostic value of non-invasive surrogate markers of PH in interstitial lung disease. The study did not show any single non-invasive measurement that correlated well with mortality outcomes. However, a raised PVR strongly predicted death within 1 year ( $p=0.001$ ), with a level of  $\geq 6.23$  Wood units being the differentiating threshold after adjusting for age, gender, composite physiological index and diagnosis of idiopathic PF ( $p=0.001$ ). Right ventricular dilation on echocardiography was also a marker of prognosis. Interestingly, these mirror findings on prognostic markers in iPAH,<sup>19 20</sup> and these findings were relevant in all patients with diffuse interstitial lung disease, irrespective of the severity of fibrosis or the underlying condition.

The findings of Corte and colleagues will help create a prognostic indicator that is useful for both patient and physician

alike. Results from a right heart catheterisation might be combined with prognostic biomarkers from less invasive methods such as CD62e endothelial microparticle levels.<sup>21</sup>

One example of such an approach is demonstrated by the REVEAL study.<sup>22</sup> In a retrospective assessment of 2716 patients with PH, multivariable analyses showed that mortality was predicted by renal dysfunction, PH associated with connective tissue disease, WHO functional class III, mPAP, resting systolic blood pressure and heart rate, 6MWD, brain natriuretic peptide, percentage predicted carbon monoxide diffusing capacity and pericardial effusion on echocardiogram. These were used to derive a prognostic equation that was validated by a bootstrapping technique.

More prospective and follow-up trials are needed, but the ultimate aim is to create a comprehensive tool to risk-stratify patients appropriately. This will enable us to optimise targeted treatment on an individual basis as well as help us identify patients who should, if otherwise suitable, be urgently placed on the lung transplant waiting list.

### LUNG TRANSPLANTATION

It has been >25 years since the first successful single-lung transplant was performed.<sup>23</sup> The subsequent years have seen lung transplantation become established as a viable treatment option for many patients with severe end-stage lung disease and a life expectancy of <2–3 years that have received maximal medical treatment.<sup>24 25</sup> Significant advances have been made in improving the outlook in the immediate postoperative period, but long-term prognosis remains limited by the development of chronic lung allograft dysfunction.

Chronic lung allograft dysfunction manifests clinically with a progressive loss of lung function termed bronchiolitis obliterans syndrome (BOS); this is the clinical correlate of the pathological diagnosis obliterative bronchiolitis (OB). The aetiology of OB is believed to be mediated by chronic alloimmune damage, although a number of non-alloimmune insults also increase the risk of developing OB.<sup>26</sup>

The pathological lesion of OB causes obstruction of small and medium sized airways due to an excessive fibroblastic response that produces deposition of extracellular matrix (ECM), leading to aberrant epithelial repair and airway remodelling. Although progress has been made, the cellular mechanisms behind the aetiology of OB remain elusive.

### The influence of the airway epithelium on lung immunity

The airway epithelium plays a major role in lung host defence and is the focus of the insults that drive chronic lung allograft dysfunction. In addition, the secretory products of the airway epithelium, by producing inflammatory cytokines and growth factors, may have a role in immune regulation.<sup>27</sup> It has previously been shown that airway epithelial cells can drive the differentiation of dendritic cells (DCs) from monocytes.<sup>28</sup> As DCs may play a role in driving immune-mediated airway damage, airway epithelium may be important in influencing the extent of the alloimmune response in the transplanted airway.

With this in mind, Ward *et al* investigated the potential for bronchial epithelial cells to drive the production of DCs from monocytes in clinically stable lung transplant recipients.<sup>29</sup> By applying epithelial cell conditioned media to CD14 monocytes the investigators assessed the effect on their differentiation into DCs. This was then compared with cells cultured without epithelial cell conditioned media and with monocyte-derived macrophages. The study shows that the secretory products of bronchial epithelial cells favour the differentiation of monocytes

into macrophage-like cells, at the expense of DC differentiation. This occurred both morphologically with decreased expression of DC markers (CD1a) and raised markers (CD14) of macrophages, as well as functionally with greater phagocytic activity of the macrophage-like cells.

This study suggests that the microenvironment in the airway of stable lung transplant patients, generated at least in part by the bronchial epithelium, may help restrain airway DC development and limit potential alloimmunity. It has been suggested that the default production of macrophages is appropriate in the human airway as, together with an intact epithelium, they represent the first line of defence in lung innate immunity.<sup>30</sup>

### Airway epithelial cell responses in the transplanted lung

The link between innate immune responses such as that of airway epithelium and adaptive immune responses from 'professional' immune cells appears critical in driving the remodelling that occurs in the transplanted lung. An example comes from the observation that the airway injury caused by bacterial or viral infections is associated with an increased risk of developing BOS.

As the epithelium is injured it becomes disrupted and loses its barrier function. Attempted repair responses occurring in the injured epithelium may be critical in the pathophysiology of BOS.<sup>31</sup> Animal models have also suggested that epithelial injury and the inability to re-establish an intact epithelium may lead to excessive deposition of ECM.<sup>32</sup> Epithelial cells can respond to injury in a number of ways that include repair, necrosis, apoptosis and epithelial to mesenchymal transition (EMT), the latter being a process in which the cells assume the morphological and functional characteristics of mesenchymal cells including increased production of ECM.<sup>33</sup>

Borthwick *et al*<sup>34</sup> proved that human airway epithelial cells from lung transplant recipients can undergo EMT and may be an underlying mechanism behind aberrant airway remodelling in BOS. This study demonstrated that transforming growth factor  $\beta$  (TGF $\beta$ ), a driver of fibrosis with increased levels of expression in patients with OB,<sup>35</sup> was able to induce EMT. This process was significantly accentuated by combining TGF $\beta$  with tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), a proinflammatory stimulus. The combination demonstrated the presence of increased mesenchymal markers and decreased epithelial markers. More importantly, these cells obtained the functional characteristics of myofibroblasts, including the ability to invade collagen and deposit ECM.

Another study from the same group demonstrated that co-treatment with TGF $\beta$  and TNF $\alpha$  or interleukin 1 $\beta$  (IL-1 $\beta$ ) but not IL-8 accentuates EMT compared with TGF $\beta$  alone.<sup>36</sup> The induction of EMT was associated with accelerated epithelial wound closure, albeit in a highly dysregulated manner. These observations are supported by a study showing an association between BOS and the absence of immunosuppression of peripheral blood interferon  $\gamma$  and TNF $\alpha$ .<sup>37</sup> Together these papers raise the possibility that cross-talk between TGF $\beta$  and proinflammatory intracellular pathways plays an important role in the development of BOS, highlighting the potential of a novel route for the diagnosis and treatment of BOS that should be explored further. An intriguing possibility is that these findings may have relevance to other diseases of the small airways. Small airway epithelium undergoes more rapid and complete EMT, which may be the reason why BOS is predominantly a small airway disease.<sup>38</sup> Doerner and Zuraw<sup>39</sup> confirmed that TGF $\beta$  can induce EMT and noted that pretreatment with corticosteroids did not influence this transition. They posited that since

TGF $\beta$  expression is strongly associated with asthma, EMT may contribute to the airway remodelling process that is seen in chronic asthma.

### Patterns of ventilation in lung transplant recipients

Patients with chronic respiratory diseases suffer from dyspnoea for many years. An important postoperative outcome in lung transplant recipients is their ability to resume breathing in a comfortable and effective fashion as compared with the chronic changes in breathing pattern present prior to transplant. Wilkens *et al*<sup>40</sup> conducted a study to investigate the different patterns of ventilator adaptation in chronic respiratory failure. They looked specifically at patients with PF, cystic fibrosis (CF) and COPD, and compared the different characteristics of the diseases as well as the reversibility of the abnormal ventilator pattern after transplant.

The study showed that each disease demonstrated a different breathing pattern to cope with the final stages of chronic respiratory failure. The main change in patients with COPD was a reduced duty cycle (inspiratory time/total respiratory cycle time), while patients with PF and CF exhibited increased breathing frequency and decreased tidal volume. The lack of respiratory reserve is postulated to be the reason why patients with PF and CF are prone to respiratory failure at an earlier stage compared with patients with COPD. The key finding though is the fact that lung transplantation restores the patient's breathing to a normal pattern very rapidly.

The aim behind any lung transplant is to not only provide prognostic benefits, but to improve quality of life as well. Unfortunately, daily physical activity can remain substantially reduced after lung transplantation compared with healthy cohorts.<sup>41</sup> The findings by Wilkens and colleagues are useful in the setting of utilising pulmonary rehabilitation for patients both before and after lung transplantation in order to elicit optimal clinical response. A recent systemic review<sup>42</sup> concluded that there was evidence to support structured exercise training to improve exercise capacity and skeletal muscle strength in patients following lung transplant, although it noted the need for further studies to determine optimal guidelines for exercise prescription.

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