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Review article

Lung function in pulmonary hypertension

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ABSTRACT

Breathlessness is a common symptom in pulmonary hypertension (PH) and an important cause of morbidity. Though this has been attributed to the well described pulmonary vascular abnormalities and subsequent cardiac remodelling, changes in the airways of these patients have also been reported and may contribute to symptoms. Our understanding of these airway abnormalities is poor with conflicting findings in many studies. The present review evaluates these studies for the major PH groups. In addition we describe the role of cardiopulmonary exercise testing in the assessment of pulmonary arterial hypertension (PAH) by evaluating cardiopulmonary interaction during exercise. As yet, the reasons for the abnormalities in lung function are unclear, but potential causes and the possible role of inflammation are discussed. Future research is required to provide a better understanding of this to help improve the management of these patients.

1. Introduction

Pulmonary hypertension (PH) is associated with considerable morbidity and significant mortality [1–4]. This has been attributed to progressive right ventricular dysfunction due to chronic pressure overload causing myocardial hypertrophy and dilatation [5]. Symptoms are improved by medical therapies which reduce pulmonary vascular resistance and improve cardiac output for patients with pulmonary arterial hypertension (PAH) and some patients with chronic thromboembolic pulmonary hypertension (CTEPH) [6]. This, alongside improvements in general care, has coincided with a marked improvement in mortality with a 1 year survival for idiopathic PAH (IPAH) patients of 91–93% and a 5 year survival of 59–66% [7–9], compared to a median survival of 2.8 years and a 5 year survival of 24% prior to the advent of these therapies [10]. However, medical therapies are not curative. Many patients will remain symptomatic despite maximal treatment and can expect symptoms to increase as the disease progresses. In contrast, patients with PH due to other causes have no additional therapies to aid symptoms, with management directed at the underlying cause [6].

Breathlessness is the main symptom in PH, experienced almost universally in more advanced disease [11]. This is a complex symptom that can be caused by abnormalities of the cardiovascular, respiratory and neuromuscular systems in a variety of diseases [12,13]. Though the abnormalities of the cardiovascular system in PH are well described [5], it is unclear to what extent the respiratory system is affected. The abnormal pulmonary vessels could affect the function of their adjacent airways and contribute to symptoms. If the airways were affected in addition to the pulmonary vessels, this could represent another treatment target for a symptomatic group that remain difficult to treat despite the availability of newer drugs.

Lung function assessment provides important information about the physiology of the lung and useful insight into a variety of

Abbreviations: CHD-APAH, pulmonary arterial hypertension associated with congenital heart disease; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; CTD-APAH, pulmonary arterial hypertension associated with connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, carbon monoxide diffusing capacity; ELISA, enzyme-linked immunosorbent assay; ET-1, Endothelin-1; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IL, interleukin; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; $PETCO_2$, end tidal partial pressure of carbon dioxide; PH, Pulmonary hypertension; TLC, total lung capacity; TNFα, tumour necrosis factor alpha; VCO_2, carbon dioxide production; V_E, minute ventilation; VO_2, oxygen consumption.

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disease processes [14]. This article aims to review the existing, often conflicting, literature in PH focusing on Group 1 – PAH, with coverage of the other major groups: Group 2 – PH due to left heart disease, Group 3 – PH due to chronic lung disease and Group 4 – CTEPH [15]. Group 5 – PH with unclear or multifactorial mechanisms has not been covered due to its heterogeneity and rarity of conditions. Cardiopulmonary exercise testing (CPET) has been covered in its own right as a more novel investigation, but as yet data is limited and so the review is restricted here to Group 1 – PAH. The potential role of inflammation and vasoactive mediators is discussed, and future direction for research suggested.

2. Group 1 – Pulmonary arterial hypertension

2.1. Idiopathic pulmonary arterial hypertension

2.1.1. Lung volumes

20-50% of patients with IPAH have lung restriction, defined as a total lung capacity (TLC) of less than 80% of predicted values [16,17]. The overall mean reduction in TLC is to 64–91% of predicted values in some studies [18–20], while others have reported that TLC is normal [21,22]. This variation may be in part due to the significant proportion of patients with unaffected lung volumes in IPAH. The most marked reductions in TLC have been reported in smaller case series which are more susceptible to the inclusion of more extreme cases [18,19]. The true overall abnormality is likely to be more modest as found in larger studies [20]. Studies that have reported a normal TLC also found a reduction in vital capacity that was offset by an increase in residual volume [21,22]. Thus while patients with IPAH may have lung restriction, TLC may normalise due to hyperinflation that can occur with airway obstruction in more severe disease [22].

The cause of lung restriction in patients with IPAH is unclear. While parenchymal changes in other lung conditions cause lung restriction, this does not occur in IPAH [23]. An explanation could be that the hypertrophied blood vessels may have a direct physical effect with encroachment resulting in a loss of distensibility through mechanical pressure on the airways. Some older, small studies have found reduced lung compliance in IPAH in keeping with this, but this was not associated with a reduction in lung volumes [24]. The hypertrophied pulmonary vessels, in addition to the ensuing cardiomegaly, could result in displacement of lung tissue within the thoracic space. While this is associated with lung restriction in PH due to left heart disease [25,26], this has not been evaluated in IPAH. The cause of these changes is thus currently unclear, while the impact on patients' symptoms has not been assessed.

2.1.2. Spirometry and expiratory flow

20-40% of patients with IPAH have airway obstruction based on a forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) ratio of less than 70% [19,27]. The overall mean FEV_1/FVC ratio is significantly reduced at 76% compared to 84% in controls ($p < 0.001$) [22]. The fact that many studies have reported an overall mean greater than 70% is therefore unsurprising as many patients will have a normal FEV_1/FVC ratio [17,18,20,21,27]. However the conclusion that there is no evidence of airway obstruction in IPAH is an oversimplification [17,21]. Spirometry is a poor marker of peripheral airway obstruction as the peripheral airways contribute to less than 10% of total airway resistance [28]. Extensive small airway disease would therefore only lead to a small reduction in FEV_1. Measures of mid-expiratory flow are more sensitive markers of peripheral airway obstruction and small airway disease [29] and are significantly reduced in IPAH. Flow-volume curves are curvilinear in appearance as a result [20,22]. Studies that have found no evidence of airway obstruction have not utilised these measures [17,21]. Therefore whilst the majority of patients with IPAH may have normal FEV_1/FVC ratios, clinicians should assess flow–volume curves as well to ensure adequate assessment for small airway disease has been conducted.

As with lung volumes the cause for these changes is unknown. While intimal and medial thickening of the pulmonary arteries is seen histologically, whether these encroach on the adjacent airways to affect airflow and cause airway obstruction is unknown [23]. Inflammation and mucus plugging can cause airway obstruction in other lung diseases, though histological evidence of this occurring in IPAH is limited [30]. However, systemic inflammation is a feature of IPAH with increasing evidence that this may play an important role in its pathogenesis [31]. Lung tissue analysis in IPAH has demonstrated the presence of perivascular inflammatory cell infiltrates consisting of T cells, B cells and macrophages [32], while recent pathology specimens of explanted lungs in PAH due to a range of causes demonstrated perivascular and interstitial inflammation in addition to the known vascular changes [23]. In IPAH patients, the use of enzyme-linked immunosorbent assays (ELISA) on venous samples show that serum levels of inflammatory cytokines including interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, and tumour necrosis factor alpha (TNFα) are significantly elevated when compared to controls [33,34]. These may play an important role in arterial remodelling [35]. Protein movement from the systemic circulation into the airways has been shown to occur, and this can increase in the presence of inflammation due to effects on epithelial permeability [36,37]. If an overspill of these inflammatory mediators and cells into the airways occurs, the resulting airway inflammation could account for the airway obstruction seen.

Similarly an overspill of vasoactive mediators into the airways could cause bronchoconstriction. Endothelin-1 (ET-1) is thought to play a key role in the vascular changes seen in PAH as it is a potent vasoconstrictor with the ability to stimulate the proliferation of pulmonary arterial smooth muscle cells [38]. Specific radioimmunoassay has demonstrated raised venous plasma levels of ET-1 in IPAH, associated causes and secondary causes when compared to healthy volunteers [39]. ET-1 can also cause bronchoconstriction both in vitro [40], and in vivo when inhaled by asthmatics [41]. ET-1 has also been found in bronchoalveolar lavage samples of COPD patients [42], and in greater concentration in patients with cystic fibrosis in induced sputum samples [43]. Likewise, the production of nitric oxide by endothelial cells is decreased in PAH [44]. Nitric oxide induces vasodilatation and can also cause airway dilatation [45]. Whether levels of inflammatory mediators and vasoactive mediators are increased in the airways is however unknown.

Though the airway abnormalities described may be viewed as mild, this leads to exercise related dynamic hyperinflation which may contribute to symptoms and reduced exercise capacity [46,47]. Studies regarding treatment of airway obstruction are limited, and it is unknown if bronchodilators can improve symptoms [48].

2.1.3. Gas transfer

Three quarters of IPAH patients will have abnormal gas transfer (carbon monoxide diffusing capacity (DLCO) of less than 80% predicted) with a mean across studies of 59–71% of predicted values [17,19,20,22,49]. When adjustments have been made to account for smoking, DLCO has remained abnormal suggesting a true abnormality in IPAH [17]. It is unlikely that this reduction in DLCO can be explained purely by ventilation-perfusion mismatch, as the alveolar volume and TLC at rest are very closely matched [17]. Further analysis of gas transfer in patients with IPAH demonstrates that both pulmonary membrane diffusion capacity and the pulmonary