Final Report Summary - EDPAH (Mechanisms of Exertional Dyspnea in Patients with Idiopathic Pulmonary Arterial Hypertension)

Study # 1

Rationale:

Exertional dyspnoea is the most frequent complaint for which patients with pulmonary arterial hypertension (PAH) seek medical attention. It progresses relentlessly as the disease advances, contributing importantly to an impoverished quality of life. Previous studies on the mechanisms of exertional dyspnoea in PAH have largely and mostly focused on the cardiovascular determinants of respiratory discomfort. However, respiratory mechanics abnormalities could contribute to and aggravate exertional dyspnoea in these patients. For instance, PAH patients may exhibit reduced expiratory flows at low lung volumes at spirometry (namely instantaneous forced expiratory flows measured after 50% and 75% of the forced vital capacity (FVC) has been exhaled [FEF50% and FEF75%] lower than predicted), despite a preserved forced expiratory volume in 1 s/FVC ratio (FEV1/FVC). Several studies have shown that such a finding could be common in certain PAH cohorts, have related it to incidental descriptions of airway wall thickening with lymphocytic infiltration in PAH and proposed several other speculative explanatory mechanisms, either biological or mechanical. Whatever its cause, reduced expiratory flows at low lung volumes imply that the operating tidal volume (VT) range becomes closer than normally to residual volume (RV) mostly through an increase in RV (elevated RV/total lung capacity (TLC) ratio, RV/TLC). The reduced difference between forced and tidal expiratory flows promotes dynamic lung hyperinflation [DH, a progressive decrease in inspiratory capacity (IC)] under conditions of increased ventilatory demand. DH increases the mechanical inspiratory load that the respiratory muscles must overcome to produce ventilation (VE), places the diaphragm at mechanical disadvantage, and reduces the ability of VT to expand appropriately during exercise, thus imposing ‘restrictive’ mechanics. Dyspnoea ensues, as clearly shown in flow-limited patients with chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) during exercise.

Hypotheses:

We hypothesised that this sequence of events would occur in PAH patients exhibiting reduced expiratory flows at low lung volumes at spirometry. To test this hypothesis, we examined the impact of exercise-induced increased ventilation on operating lung volumes in young non-smoking non obstructive PAH patients. We also aimed at studying the putative contribution of DH and the corresponding mechanical constraints on VT expansion to exertional dyspnoea in this setting.

Summary overview of results:

Twenty-five young (38 ± 12yr old), non obese (normal body mass index), non-smoking PAH patients with no evidence of spirometric obstruction and 10 age-matched non-smoking healthy subjects performed a CPET to the limit of tolerance. Ventilatory pattern, operating lung volumes [derived from inspiratory capacity (IC) measurements], and dyspnoea intensity (Borg scale) were assessed throughout CPET.
IC decreased (i.e. DH) progressively throughout CPET in PAH patients (average 0.15 L), whereas it increased in all the healthy subjects (0.45 L). Among PAH patients, 15 (60 %) exhibited a decrease in IC throughout exercise (average 0.50 L), whereas in the remaining 10 patients (40 %) IC increased (average 0.36 L). Dyspnoea intensity and ventilation were greater in PAH patients than in controls at any stage of CPET, whereas inspiratory reserve volume was lower.

Conclusions:

This study is the first to examine the impact of potential DH-induced critical mechanical constraints on the intensity of dyspnoea in young non-smoking patients with idiopathic and heritable PAH undergoing symptom-limited incremental CPET. It confirms that reduced expiratory flows at low lung volumes at spirometry exist in a certain proportion of idiopathic and heritable PAH patients (60 %) despite a preserved FEV1/VC ratio. It demonstrates that these abnormalities promote DH in response to the exercise-related increase in ventilation that can be magnified by ventilation / perfusion mismatching and other factors. Although exercise-related dyspnoea in PAH has important cardiovascular determinants, our results indicate that abnormal dynamic ventilatory mechanics can contribute to the build-up of this symptom during exercise. Of note, the changes in operating lung volumes that we observed (e.g. reduction of both IC/TLC and IRV/TLC) explained 50 to 60 % of the variance of the exercise-related increase in dyspnoea. This could be considered surprising given the magnitude of these changes, but probably reflects the fact that adding a mechanical burden on top of cardiovascular limitations has an exponential effect on dyspnoea.

Limitations of the project:

In the absence of oesophageal pressure measurements in this study - a choice justified by the exploratory nature of the study and our concern to keep it as close to observational as possible - we must concede that the decrease in dynamic IC may be due either to DH, inspiratory muscle weakness or fatigue, or both in combination. Regardless of the mechanism, the consistent decrease in dynamic IC seen in PAH-H is likely to be physiologically and clinically meaningful. Given the small sample size we must be careful to avoid any generalisation of our findings to the larger PAH population. Further studies that contain a larger sample size and engage oesophageal pressure measurements during exercise will be required to definitively elucidate the physiological mechanisms of the altered ventilatory mechanics seen in PAH patients.

Socio-economic impacts of the project:

The corollary of our findings is that therapeutic interventions aimed at reducing or delaying the DH-related mechanical constraints could possibly be useful add-ons to vasodilators in the management of PAH patients exhibiting reduced expiratory flows at low lung volumes. The present data are however not sufficient to reach this conclusion. Future studies will be needed to determine the exact indications and risk-benefit balance of such interventions, including bronchodilators, in the setting of PAH.

Study #2

In the absence of oesophageal pressure measurements in study # 1, we had to concede that the decrease in dynamic IC may be due either to DH, inspiratory muscle weakness or fatigue, or both in combination. To address this question, we examined the impact of potential inspiratory muscle constraint on dynamic operating lung volumes response during symptom-limited incremental cardiopulmonary cycle exercise testing (CPET) in patients with pulmonary arterial hypertension (PAH). Thirty-three young non-smoking PAH patients (idiopathic = 26; heritable = 7) with normal body mass index and no spirometric evidence of obstructive ventilatory defect (FEV1/FVC = 115 ± 10% predicted) performed a CPET to limit of tolerance. Ventilatory profile, operating lung volumes [derived from inspiratory capacity (IC) measurements] and inspiratory flow reserve (IFR), an indirect index of inspiratory muscle constraint/fatigue, were assessed throughout CPET. Twenty-two patients (67 %)
decreased IC (i.e. dynamic hyperinflation) throughout exercise by 0.50L (PAH-H), whereas the remaining patients (33 %) increased IC by 0.36L (PAH-NH). V'E and V'O2 at peak exercise were comparable between the two groups. Despite these differences in operating lung volumes response, IFR at peak exercise was not statistically different between PAH-H and PAH-NH (1.9 ± 1.0 versus 2.0 ± 0.8L/s p = 0.7). Both PAH-H and PAH-NH achieved inspiratory tidal flows that approached a similar percentage of the maximal available inspiratory flows (i.e. similar IFR), suggesting that the inspiratory flow-generating reserve of the inspiratory muscles at peak exercise was similar (but occurred at different operating lung volumes). The presence of inspiratory muscle constraint / fatigue and its contribution in modulating the dynamic operating lung volumes response to CPET is unlikely.

Of course these are encouraging results but they give us only an indirect picture of the real situation. To better address the question of the presence or absence of inspiratory muscle weakness / fatigue and its impact on operating lung volumes and exertional dyspnoea in PAH patients, we are actually measuring respiratory mechanics via oesophageal catheter in a selected group of PAH previously included in study # 1. Three patients have already been recruited and evaluated, so far. We aim at recruiting 10 - 12 subjects, and are confident that we will be able to end study # 2 by the end of June 2013.

The aim is to show that during IC measure the oesophageal pressure (which reflects the pleural pressure) remains constant, so that IC changes during exercise would reflect the development of DH rather than the development of inspiratory muscle fatigue.

As the results of study # 2 will be available and published, the REA will be informed.

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