PNEUMOLAB PROCEEDINGS

MINERVA MED 2014;105(Suppl. 1 to No. 1):1-7

Pulmonary hypertension in COPD and lung transplantation: timing and procedures

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The prevalence of pulmonary hypertension (PH) in the general chronic obstructive pulmonary disease (COPD) population is undefined because stable COPD patients do not routinely undergo screening echocardiogram and right heart catheterization. Most studies published on this topic are focused on a highly selected group of patients with moderate to severe disease awaiting lung transplantation, since hemodynamic data from cardiac catheterization are part of the standard transplant evaluation. In a very recent article, Hurdman *et al*. studied the characteristics and outcomes, with a particular focus on mortality, of extensively phenotyped, consecutive patients with PH-COPD over a 9-year period. This article offers the opportunity to update the role of PH in COPD as a timer to propose lung transplantation, based on solid literature data on survival, and to select the best procedure (single or double lung transplant), since the outcome indexes based on the old GOLD classification according to FEV_1 (1-4) and the new GOLD classification (A-D) have failed in purpose to define the correct timing, due to the lack of functional (6 minutes walking test) and nutritional (Body Mass Index) data. After a revision of available literature including the recent paper of Hurdman *et al*. we conclude that the timing for lung transplantation is easy to manage in case of severe PH-COPD. On the other hand mild and moderate PH-COPD are still object of debate for therapy, procedure timing and choice and rehabilitation. In other words, we have some confirms for a little percentage of patients, whilst many doubts still exist for the rest.

KEY WORDS: Emphysema - Lung diseases, obstructive - Hypertension, pulmonary - Respiratory function tests - Lung transplantation.

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Chronic obstructive pulmonary disease (COPD) is defined in terms of airflow obstruction that results from an inflammatory process affecting the airways and lung parenchyma. Different inflammatory mediators can have local and systemic ac-

tivities and clinical consequences.[1] Changes in pulmonary vessels represent an important component of the disease. Alterations in vessel structure are very common,[2] and abnormalities in their function impair gas exchange and result in pulmonary hypertension (PH).

PH is defined as a mean pulmonary artery pressure (mPAP) higher than 25 mmHg, as measured by right heart catheterization at rest.[3] Pulmonary arterial hypertension (PAH) and pulmonary venous hypertension (PVH) are traditionally distinguished on the basis of pulmonary arterial wedge pressure (PAWP) with a cut-off of 15 mmHg. In 2008, the Dana Point Symposium on Pulmonary Hypertension classified COPD-associated PH into Group 3 "Pulmonary hypertension associated with lung disease and/or hypoxemia".[4] Severe PH-COPD, arbitrarily defined by a resting mPAP>40 mmHg, is a rare nosological entity, occurring in about 1% of patients with chronic respiratory failure related to COPD.[5]

There are no International Guidelines in literature that define with a pre-set algorithm the correct definition of PH "out of proportion" in COPD. A German Consensus describe that in patients with chronic lung disease, the presence of PH should be suspected when the symptoms are more severe than expected based on lung function data, or when signs of right heart dysfunction are present. Profound hypoxemia, hyperventilation, or low DLCO values can be indicators of PH. The cut-off described was a value of mPAP of 35 mmHg calculated with right heart catheterization.[6]

The prevalence of PH in the general COPD population is undefined because stable COPD patients do not routinely undergo screening echocardiography and right heart catheterization. Most studies published on this topic are focused on a highly selected group of patients with moderate to severe disease awaiting lung transplantation because hemodynamic data from cardiac catheterization are part of the standard transplant evaluation. These studies have found that PH is a common feature in advanced COPD. An interesting study evaluating patients with very severe COPD (mean FEV_1 <27% predicted), detected a prevalence of PH of 90.8% by using a definition for pulmonary hypertension of a mPAP higher than 20 mmHg. The majority (61.4%) of the patients had a elevated PAWP of more than 12 mmHg, suggesting the cause of their PH be related, at least in part, to underlying cardiac abnormalities.[7] A second study followed 215 patients evaluated for lung volume reduction surgery or lung transplantation (mean FEV_1 24% predicted). Using a definition of PH as mPAP>25 mmHg (patients with elevated PAWP were excluded), the prevalence of PH resulted 50.2%.[8] The largest study to date evaluated 4930 patients listed for lung transplantation with the primary diagnosis of COPD. PH was defined using WHO group 1 PAH criteria (mPAP >25 mmHg with PCWP<15 mmHg) and PVH as mPAP>25 mmHg with PCWP>15 mmHg. The prevalence of PAH in this cohort was reported to be 31% with an additional 17% having PVH.[9]

In a very recent article Hurdman *et al.*[10] studied the characteristics and outcomes, with a particular focus on mortality, of extensively phenotyped, consecutive patients with PH-COPD over a 9-year period. This article offered the opportunity to update the role of PH in COPD as a timer to propose lung transplantation, based on solid literature data on survival, and to select the best procedure (single or double lung transplant), since the outcome indexes based on the old GOLD classification according to FEV_1 (1-4) and the new GOLD classification (A-D) have failed in purpose to define the correct timing, due to the lack of functional (6 minutes walking test) and nutritional (Body Mass Index) data.[11-15]

Older studies demonstrated different survival in patients PH-COPD.[16-22] Bishop divided COPD patients in four groups depending on mPAP: 1) mPAP<25 mmHg; 2) between 25 and 35 mmHg; 3) between 35 and 45 mmHg; and 4) >45 mmHg. Survival curves resulted different, with a survival in the <25 mmHg group almost comparable to that of the patients with normal mPAP values and a 5 years mortality of about 90%

in COPD patients of the forth group (mPAP >45mmHg) who underwent lung transplantation. In the two intermediate groups, mPAP was not conclusive for timing and procedure indication.[16] Moreover, Weitzenblum *et al.* demonstrated that patients with COPD and PH have shorter survival than patients with normal PAP values [22] and Burrows *et al.*[18] showed that survival was inversely related to pulmonary vascular resistance (PVR). In a 15-year follow-up study performed on 200 patients, Traver *et al.*[21] showed that, after an age adjustment, the presence of cor pulmonale was one of the most accurate predictors of mortality. Unluckily these studies were conducted before the introduction of long-term oxygen therapy (LTOT), a cornerstone treatment for chronic respiratory failure in COPD. Nevertheless, a recent study conducted in 84 patients receiving LTOT, has been confirmed that PAP is the single best predictor of mortality. The five-year survival was 36% in patients with PAP>25 mmHg, whereas in patients with PAP<25 mmHg survival was 62%.[20] Furthermore, echocardiographic signs of right ventricular dysfunction [17] and ECG signs of right ventricular hypertrophy or right atrial overload were also predictive of survival in COPD.[19]

Hurdman adds precious information in terms of phenotyping as the survival has been studied on the basis of mPAP, age, DLCO, SvO_2 and WHO functional class. These parameters were analyzed in COPD patients divided in two groups on the basis of their mPAP values: between 25 and 40 mmHg, or >40 mmHg. Those with severe PH-COPD (mPAP>40 mmHg), exhibited a 1- and 3-year survival of 70%, and 33%, respectively, whilst 1- and 3-year survival rate was of 83%, and 55% in patients with mild to moderate PH-COPD (mPAP>25 mmHg, <40 mmHg) (P=0.011). ROC curve analysis confirmed a mPAP of 40 mmHg to be the optimal threshold (sensitivity 68%, false-positive rate 45%) for determining survival.[10]

Multivariate analysis demonstrated that age, DLCO, SvO_2 and WHO functional classes are all independent predictors of survival. ROC curve analysis found the following thresholds for predicting survival (P=0.001): an age of 73 years (sensitivity 58%, false-positive 26%); 27% of predicted values for DLCO (sensitivity 69%, false-positive 32%); and 65% for SvO_2 (sensitivity 80%, false-positive 46%). Survival at three years in patients with PH-COPD in WHO functional class III at diagnosis was 47%, superior to that of 20% for patients presenting in WHO functional class IV (P=0.001).[10]

Despite the use of drugs currently approved for PAH in patients with COPD is not recommended by Guidelines, forty-three patients with severe PH-COPD were treated in the Hurdman study compassionately with therapies currently indicated for PAH patients in the first group of the Dana Point classification; first-line treatment was phosphodiesterase type 5 (PDE-5) inhibitors in 31 patients, endothelin receptor antagonist (ERA) in 10 patients, s.c. treprostinil in one patient and nebulized iloprost in one patient. Clinical improvement was defined as a reduction of 20% in pulmonary vascular resistance (PVR) or improvement in WHO functional class. At follow-up, right heart catheterisation data were available for seven patients and showed a reduction of the PVR values of >20% in four patients. Four patients experienced an improvement in WHO functional class after 42 months of treatment. The eight patients who demonstrated clinical improvement had superior survival when compared to the 35 patients receiving pulmonary vascular treatment without objective improvement, even though no significant difference was detected in terms of demographics, hemodynamic, high resolution CT scan and respiratory functional tests between the two groups.[10]

The study of Hurdman *et al.* is interesting and elegant but, because of the low number of patients, survival has been examined for just two groups: severe PH COPD (mPAP >40 mmHg) and all the other patients (mild and moderate PH).[10] From a prognostic point of view a mPAP 25-30 mmHg results significantly different than a mPAP 35-40 mmHg. No evaluation on survival was done using the German Consensus cut-off for "out of proportion" PH.

Similarly, even if the analysis of the result of the parameters (age, DLCO, SvO_2, WHO class) in this dichotomous subdivision offers some advantages from a statistical point of view, the cut-off used are difficult to use in the clinical practice. For example, the age category has a cutoff of 73 years, practically useless in since patients in waiting list are indicatively less than 65. The same for DLCO > or <27% and WHO class. The utility seems to be a little greater considering SvO_2 values: 65% may represent an acceptable cut off with patients having higher values a better outcome in terms of survival, and patients with lower values a much worse survival rate.

Lung transplantation remains the only effective therapeutic strategy for end-stage lung disease in selected patients.[23] However, the limited number of available grafts represents the major limitation to its clinical application, despite several strategies have been suggested to overcome this problem.[24] When studying patients for lung transplantation, at least two questions must be answered: "Is the timing correct?", and, "What is the correct procedure (single or double lung transplant)?"

So far, the correct timing in COPD is given mainly by the BODE index [25] whilst the choice of the procedure in COPD [26] and in fibrosis [27] is still an open debate, in particular because of the recent emerging procedures of organ procurement such as *ex vivo* lung reperfusion [28] and non heart beating donors.[29]

The Hurdman study offers some answers, by remarking that patients with mPAP>40 mmHg, SvO_2<65 mmHg, WHO class IV and DLCO <27% can be referred to a lung transplantation center in the correct timing. On the other hand it leaves open another question: for a too wide category of patients (mPAP 25-40 mmHg, SvO_2 >65%, WHO class<IV and DLCO>27%) should such a dramatic surgical procedure be proposed to a so wide category of patients? It is noteworthy that 50% patients candidate to surgical lung volume reduction or transplantation with a FEV_1<24% have mPAP values of 25-35 mmHg.

A mild PH in COPD is likely characterized by a better survival as proposed by Bishop in his historical article [16] and the same could probably be said for patients with mild reduction of DLCO. This is particularly important since in different studies we cited, 91% of patients with FEV_1 <27% of predicted values had mPAP>20 mmHg, but just 5% showed a mPAP>35 mmHg,[7] and only 2.7% had a mPAP>45 mmHg. To resume, the prevalence of mild to moderate PH in COPD is high, and how we should behave in case of mild to moderate PH-COPD is still a matter of open discussion.

Moreover, a great problem in Intensive Care Units is the post-surgical management in case of single Lung Transplant in COPD: in fact in PH-COPD patients immediately after transplantation almost all the blood flow is directed to the transplanted lung with high risk of reperfusion syndrome, while all the ventilation is directed to the more compliant low perfused lung (native COPD). In case of reperfusion edema, the risk is to have a transplanted lung perfused and unventilated and a native COPD lung ventilated but unperfused. The mPAP values proposed as cut-off for the choice of the procedure is conventionally 30-35 mmHg, but this is an empirical behavior that needs more data.

Another problem is the following: if the BODE index is at the moment the gold standard for timing in lung transplantation, and if rehabilitation allows us to delay the timing and to prepare the patient to surgery, how can we manage rehabilitation in PH associated to COPD?[30] The optimal exercise training program remains currently unknown. Slow, incremental exercise protocols at low intensity and short duration are often used initially. On the basis of observed hemodynamic responses to exercise in this patient population, it is prudent to avoid interval training because of the associated rapid changes in pulmonary hemodynamics and risk of syncope. On the basis of symptoms and heart rate/oxygenation response, the intensity and duration of exercise may be advanced as tolerated.[31]

However, the target level for exercise training is generally kept at a submaximal level. Although light-intensity resistance exercise may be included, this is generally performed only when the patient can comply with appropriate breathing patterns to avoid the Valsalva-type maneuvers.[32]

Historically, clinicians may have advocated the practice of avoiding strengthening exercises performed with arms raised above the head or shoulders. There is no evidence to support this practice and currently no restrictions should be applied for upper or lower extremity strengthening exercises. Range of motion exercises and flexibility training can also be performed safely by these individuals. Blood pressure, pulse rate, and oxygen saturation are monitored during exercise. Standards of care and suspension of exercise are implemented if the patient develops chest pain, lightheadedness, palpitations, hypotension, or syncope. Cautious training, usually forbidden to this kind of patients, could increase survival acting on BODE index parameters (mMMC and 6MWT).[33] Rehabilitation is a new intriguing field in PH patients. Recent data validated the role of aerobic exercise training on function and quality of life in patients with World Health Organization group 1 PH.[34, 35]

Finally, can we use therapies currently indicated for PAH in PH-COPD? Usually it is not a good choice as we risk to interrupt a pathophysiologic compensation of the perfusion/ventilation imbalance. Many studies were performed in COPD patients with mild-moderate PH to test the effects of drugs developed for PAH in this case. Unfortunately, up to date, even if no one showed a clinically relevant V/Q alteration, no improvement in respiratory outcomes was obtained.[36-38] Nevertheless, the Hurdman data reveal the presence of a subgroups of patients who exhibit a clinical response to pulmonary vascular therapies used in PAH. This observation suggests that in some patients vascular response could be stronger than what we expect in accordance to pulmonary impairment, so only in this case, the use of these therapies might be considered. However, since the presence of PH in COPD is characterized by high mortality, it is desirable that in the future a specific treatment for this condition becomes available.

In conclusion, timing for lung transplantation is easy to manage in case of severe PH-COPD. On the other hand mild and moderate PH-COPD are still object of debate for therapy, procedure choice and rehabilitation. In other words, we have some confirms for a little percentage of patients, whilst many doubts still exist for the rest.

Riassunto

Ipertensione polmonare nei pazienti affetti da BPCO e nei trapianti di polmoni: tempistiche e procedure

La prevalenza dell'ipertensione polmonare (*pulmonary hypertension*, PH) tra i pazienti affetti da broncopneumopatia cronica ostruttiva (BPCO) non è nota dal momento che questi pazienti non sono sottoposti in modo sistematico alla valutazione ecocardiografica ed al cateterismo destro. La maggior parte degli studi presenti in letteratura ha valutato pazienti estremamente selezionati, come quelli in lista trapianto, dal momento che il cateterismo cardiaco viene eseguito di routine in questo caso. Hurdman *et al.*, in uno studio da poco pubblicato, hanno esaminato, in un follow-up di 9 anni, le caratteristiche e i risultati clinici, inclusa la mortalità, di pazienti ben fenotipizzati affetti da BPCO ed ipertensione polmonare. L'articolo di Hurdman *et al.* offre l'opportunità di una revisione della letteratura relativa a questo ambito, in particolare con l'obiettivo di: 1) valutare il momento più corretto per proporre il trapianto polmonare, alla luce di solidi dati di letteratura sulla mortalità; 2) scegliere la procedura più adeguata (trapianto di polmone singolo *vs.* polmone doppio), dal momento che i risultati clinici fondati sia sulla vecchia che sulla nuova classificazione GOLD, basate sul solo FEV_1 (1-4) la prima e su FEV_1, impatto della malattia e riacutizzazioni (A-D) la seconda, hanno fallito nel definire il corretto timing del trapianto per la mancanza di dati funzionali (test del cammino dei 6 minuti) e nutrizionali (Body Mass Index). Dopo una revisione della letteratura disponibile, incluso lo studio di Hurdman *et al.*, concludiamo che il corretto timing per il trapianto è semplice da valutare in caso di grave ipertensione polmonare associata alla BPCO. Al contrario la gestione dei pazienti BPCO con ipertensione da lieve a moderata è ancora dibattuta in termini di corretto trattamento medico, scelta del momento e del tipo di trapianto ed utilità della riabilitazione. In altre parole abbiamo delle conferme

per una piccola parte di pazienti mentre rimangono ancora molti dubbi per tutti gli altri.

PAROLE CHIAVE: Enfisema - Malattia polmonare ostruttiva - Ipertensione polmonare - Test di funzionalità respiratoria - Trapianto polmonare.

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Conflicts of interest. — The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on February 3, 2014.
Accepted for publication on February 4, 2014.