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Seasonal Influenza Guidelines update

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Seasonal Influenza A and B virus infection frequently causes epidemics, that are associated with significant morbidity and mortality. Uncomplicated influenza usually presents with acute onset of respiratory and systemic signs and symptoms, such as rhinorrhea, sore throat, nonproductive cough, weakness with myalgia and arthralgia, gastrointestinal symptoms and fatigue with or without fever. Most common complications include pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS), invasive bacterial coinfection, embolic events, myositis and exacerbation of chronic disease¹³. At high risk for development of complications are young children, elderly patients, pregnant and postpartum women, immunocompromised patients, people with chronic medical conditions (e.g. COPD, heart failure, diabetes mellitus) and extremely obese patients (BMI >40)⁴. Recently, the Infectious Diseases Society of America (IDSA) published an evidence based update to the 2009 guidelines on diagnosis, treatment, chemoprophylaxis and institutional outbreak management of seasonal influenza⁵.

The rationale for diagnostic testing is to aid decisions regarding the use of antibiotics, continuation of antiviral medications, further diagnostic investigation and stricter infection prevention measures. It is stressed that laboratory confirmation of influenza is not mandatory for antiviral medication prescription, which should be administered as close to the illness onset as possible. Interestingly, history of current seasonal influenza vaccination does not influence the decision for appropriate testing or treatment.

Therefore, during high influenza activity, as defined by a high circulation of influenza A and B viruses in the local community, testing is strongly recommended for high risk outpatients who present with influenza like symptoms or its known complications and for people who present with exacerbation of their chronic medical condition, only if the test results affect clinical management. Conditional recommendation is made for testing only high risk outpatients, during low influenza activity.

During high activity, testing for influenza on admission is warranted for all hospitalized patients with acute febrile or afebrile (especially if they are immunocompromised) respiratory illness or decompensation of their chronic cardiopulmonary disease. Hospitalized patients for other conditions, who develop acute respiratory symptoms, not clearly attributed to another diagnosis, should also be tested for influenza.

Upper respiratory tract specimens and particularly nasopharyngeal specimens, which are preferred over nasal or throat swabs, should be obtained as soon as possible, ideally with 4 days from symptoms onset. Non
respiratory tract specimens (e.g., blood, urine) are not appropriate for testing. Lower respiratory tract specimens from intubated patients can also be obtained.

When available, rapid molecular assays (nucleic acid amplification tests) are preferred over the less sensitive rapid influenza diagnostic tests (RIDTs), for outpatients, as they provide their result within 30 minutes. For inpatients, reverse – transcription polymerase chain reaction (RT-PCR) improves influenza detection rate. A multiplex RT-PCR for a panel of respiratory viruses is indicated for immunocompromised hospitalized patients and can be considered for other patients, if it results in reduced further testing and decreased antibiotic use.

Antiviral treatment with a neuraminidase inhibitor (oral oseltamivir, inhaled zanamivir, or intravenous peramivir) should be administered as soon as possible. The optimal treatment duration is 5 days for oseltamivir and zanamivir and a single dose of peramivir, although prolonged administration can be considered for severe cases. Baloxavir marboxil, an oral, cap-dependent endonuclease inhibitor, has recently received an FDA approval for the treatment of acute (symptoms lasting less than 48 hours), uncomplicated influenza in patients older than 12 years. Bacterial coinfection should be appropriately investigated and empirically treated. Use of corticosteroids should be avoided, unless indicated for another reason. In addition, oseltamivir use has been proved to be safe during pregnancy.

Preexposure chemoprophylaxis throughout the period of high influenza activity is indicated for immunocompromised patients at very high risk for complications (e.g., lung transplant recipients), for whom influenza vaccinations is expected to be ineffective, and prompt treatment should be started when they become symptomatic.

Finally, during an institutional influenza outbreak, control measures and antiviral chemoprophylaxis are of paramount importance. Acute respiratory symptoms whether or not accompanied by fever, or even milder symptoms such as behavioral change, should indicate immediate empiric antiviral treatment, prior to the diagnostic test results.

REFERENCES


### TABLE 1. Antiviral Medications for Influenza Treatment and Chemoprophylaxis in Adults5-7.

<table>
<thead>
<tr>
<th>Antiviral Agent</th>
<th>Treatment</th>
<th>Chemoprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir (oral)</td>
<td>75mg twice daily</td>
<td>75mg once daily</td>
</tr>
<tr>
<td>Zanamivir (inhaled)</td>
<td>10mg twice daily</td>
<td>10mg once daily</td>
</tr>
<tr>
<td>Peramivir (intravenous)</td>
<td>600mg IV, single dose</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Baloxavir Marboxil (oral)</td>
<td>40mg, single dose (body weight 40-80kg)</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>80mg, single dose (body weight ≥80kg)</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Adamantanes5 (Amantadine and Rimantadine)</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

1. Not recommended for use in people with chronic respiratory conditions.
2. Approved for outpatients. Off label use for hospitalized patients with repeated once daily dosing.
3. Not active against influenza B viruses, high level of resistance among circulating influenza A viruses.
Assessing the budget impact of nintedanib for the treatment of idiopathic pulmonary fibrosis in the Greek healthcare setting

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SUMMARY
Idiopathic pulmonary fibrosis (IPF) is a rare, chronic lung disease with a high mortality rate. IPF affects about 5 million people worldwide with median survival being 2-5 years following diagnosis. Until recently, there was no licensed pharmacologic therapy available for IPF and patients were managed by best supportive care, that includes treatment with pirfenidone. In 2015, nintedanib was approved for the treatment of IPF. This study estimates the reimbursement of nintedanib and its budget impact on the National Organization for Health Care Services Provision (EOPPY). The budget impact of reimbursing nintedanib as part of already available treatment options corresponds to a maximum of 0.13% of annual total pharmaceutical expenditure. Therefore, it has a relatively low impact on the budget of EOPPY, while use of nintedanib was associated with a higher number of acute exacerbation events being avoided, thus providing additional cost savings to EOPPY. 


INTRODUCTION
Idiopathic pulmonary fibrosis (IPF) is a rare, chronic, and fatal interstitial lung disease characterized by dyspnoea and gradual impairment of lung function, ultimately, leading to respiratory failure (NICE 2013). IPF is slightly more prevalent in men than in women, with a mean age of presentation at 66 years (NICE 2013). Median survival is 2–5 years following diagnosis (Meltzer & Noble, 2008). IPF affects approximately 5 million people worldwide. In Europe, the estimated prevalence of IPF ranges from 1.25 to 23.4 cases per 100,000 persons (Nalysnyk et al., 2012). In Greece, the incidence of IPF has been estimated at 0.9 new cases per 100,000 persons every year (1994-2005) and the prevalence at 3.4 cases per 100,000 persons (Karakatsani et al., 2009).
The progressive nature of the disease in combination with acute exacerbations have been linked to increased morbidity and hospitalizations, resulting in substantial healthcare resource utilization. Acute exacerbations events contribute to approximately 50% of all IPF related hospital admissions (Yanni et al., 2016), while hospital mortality rate varies from 20% to 100% (Ley et al., 2014). A recently published US observational study documented 234 IPF related hospitalizations within one year at an average cost of $16,812 per stay (Yanni et al., 2016).

Until recently, there was no licensed pharmacologic therapy available for the treatment of IPF and patients were managed by best supportive care (BSC), that included oxygen therapy, opioids, corticosteroids etc. In addition, a minority of patients benefited from lung transplantation, although this treatment option was limited by the availability of donors (Kistler et al., 2014). In 2011 pirfenidone, an oral antifibrotic agent, was approved for the treatment of IPF by the European Medicines Agency. Later, in 2015, nintedanib, an oral inhibitor of tyrosine kinase receptors, was also approved for the treatment of IPF. Pivotal clinical trials have shown that nintedanib and pirfenidone slow the decline in Forced Vital Capacity (FVC), which is the primary efficacy endpoint (Raghu & Selman, 2015). A recent network meta-analysis showed that nintedanib is statistically superior compared to placebo on acute exacerbation events avoided and lung function decline (Rinciog et al., 2017). Furthermore, nintedanib reduces the rate of acute exacerbations (Richeldi et al., 2016).

Both pirfenidone and nintedanib have been designed at an orphan drug status, due to the rarity of the condition, and have been reimbursed by the National Organization for Health Care Services Provision (EOPYY) in Greece since May 20, 2014 and February 16, 2016, respectively.

This study estimates the impact on the budget of reimbursing nintedanib for patients with IPF in Greece along with pirfenidone and standard of care (BSC). Potential cost savings associated with nintedanib were assessed in terms of acute exacerbations avoided compared to currently available treatments.

**METHODS AND DATA**

We used an incident-based cohort model (Figure 1) (OECD 2016, Karakatsani et al., 2009), following IPF patients on treatment for 5 years (2018 - 2022). Each year, patients on treatment could experience either an acute exacerbation event, a serious adverse event, discontinue treatment or die. Clinical data on mortality and discontinuation rates, acute exacerbations and adverse events rates were derived from three Phase III randomized clinical trials, namely INPULSIS-I & II, (Richeldi et al., 2014), CAPACITY (Noble et al., 2011) and TOMORROW (Richeldi et al., 2011). Due to lack of clinical data directly comparing the efficacy of nintedanib and pirfenidone, a network meta-analysis (NMA) was conducted to estimate the relative effectiveness of the comparators (Rinciog et al., 2017). Parametric model extrapolation was used to estimate mortality and time to acute exacerbations (Rinciog et al., 2017). Once patients discontinued their treatment, they were deemed to BSC. To estimate the budget impact of reimbursing nintedanib in the Greek market, defined as the new drug scenario, we compared its cost to the reference scenario which is a health care environment without nintedanib, that is treatment with pirfenidone and BSC.

Direct reimbursed costs included in the analysis in euros (2018) were drug acquisition costs, cost of managing acute IPF exacerbations and cost of managing adverse events. Both clinical and cost data considered in the analysis were reviewed and validated by a key opinion leader in pulmonology to reflect clinical practice in Greece. Budget Impact Analysis was performed according to Mauskopf (ISPOR) guidelines.

**RESULTS**

Our analysis estimated that the total number of patients eligible for treatment for IPF during the study period in Greece would be 1,072, 1,478, 1,733 and 1,859 patients in 2018, 2019, 2020 and 2021 respectively, allowing for model specific mortality and discontinuation rates (Table 1). Table 1 assumes a base case IPF patient population in 2018 of 555 patients, calculated on the basis of an annual incidence of 5 cases per 100,000 persons over a population of 11,090,000 people in Greece (OECD, 2016).

To estimate the budget impact of reimbursing nintedanib in the Greek market, defined as the new drug scenario, we compared its cost to the reference scenario, that is treatment with pirfenidone and BSC.

At a Daily Defined Dose (DDD) of 2,403mg/day with cost of €55.26, pirfenidone is slightly cheaper than nintedanib (€57.70), whereas their annual costs were calculated at €21,369.90 and €22,260.50 respectively. BSC cost was calculated at €1,200.00 per patient per annum and includes the cost of one visit to a GP per month and the cost of monthly oxygen therapy (Greek legislated DRGs 2012-2017). The cost of managing diarrhea was estimated...
at €37.50 per patient per annum and is reimbursed by EOPYY for chronic diarrhea only. The cost of managing an acute exacerbation event was calculated on the basis of the diagnosis related group (DRG) code assigned for the management of acute IPF exacerbations by our expert (A24X), which refers to cases of respiratory edema and failure. Cost input data are presented in Table 2.

In order to calculate the impact on the budget of EOPYY across the insured population we estimated current and future market share of available treatment options. As a base case scenario, expert view confirmed that the market share of pirfenidone ranges at 75% and of BSC at 25% for the 2018 starting year of the BIA. This estimate may be modified upon the reimbursement of nintedanib as shown in Figure 2 (Bouros D.).

Market share assumptions for each scenario during the 5-year period were deemed as realistic by expert view despite assuming an increasing uptake for nintedanib, primarily because IPF is an orphan disease with limited available treatment options and nintedanib has a favorable safety and effectiveness profile.

The annual direct cost to EOPYY of reimbursing the two treatments on the basis of the market shares detailed
TABLE 2. Cost inputs supplied by expert and used in the Budget Impact Analysis

<table>
<thead>
<tr>
<th>Type of costs</th>
<th>Unit costs (€)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>55.26/day</td>
<td>Hospital Price minus 5% based on current legislation and official price list: Price list May 2018</td>
</tr>
<tr>
<td>Management of adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management of acute exacerbation event costs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Table 3 depicts the estimated addition to EOPYY budget of just over €1.5 million in 2018, almost €2.3 million in 2019, €2.6 million in 2020, €2.6 million in 2021 and almost €2.5 million in 2022 when comparing the new scenario (with nintedanib) to the reference scenario (without

TABLE 3. Annual direct budget impact on EOPYY of adding nintedanib to current IPF treatment (current versus new scenario), 2018-2020

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current scenario</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>€169,873</td>
<td>€317,420</td>
<td>€433,659</td>
<td>€521,838</td>
<td>€588,628</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>€ -</td>
<td>€ -</td>
<td>€ -</td>
<td>€ -</td>
<td>€ -</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>€8,324,693</td>
<td>€14,805,840</td>
<td>€19,453,637</td>
<td>€22,660,487</td>
<td>€24,854,822</td>
</tr>
<tr>
<td>Total</td>
<td>€8,494,566</td>
<td>€15,123,260</td>
<td>€19,887,296</td>
<td>€23,182,325</td>
<td>€25,443,450</td>
</tr>
<tr>
<td>New scenario</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>€67,949</td>
<td>€126,968</td>
<td>€173,463</td>
<td>€208,735</td>
<td>€235,451</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>€4,414,735</td>
<td>€7,673,370</td>
<td>€9,869,032</td>
<td>€11,342,480</td>
<td>€12,368,957</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>€5,549,796</td>
<td>€9,648,568</td>
<td>€12,463,273</td>
<td>€14,279,821</td>
<td>€15,397,813</td>
</tr>
<tr>
<td>Total</td>
<td>€10,032,480</td>
<td>€17,448,906</td>
<td>€22,505,769</td>
<td>€25,831,036</td>
<td>€28,002,222</td>
</tr>
<tr>
<td>Impact on EOPYY Budget</td>
<td>€1,537,914</td>
<td>€2,325,646</td>
<td>€2,618,473</td>
<td>€2,648,711</td>
<td>€2,558,771</td>
</tr>
</tbody>
</table>
nintedanib). This equals an addition of just over 0.08% of total pharmaceutical expenditure for 2018, almost 0.12% in 2019, 0.13% in 2020, 0.13% in 2021 and 0.13% in 2022.

The model also estimated the impact of reimbursing nintedanib on reducing healthcare resource use as a result of preventing acute exacerbation events. According to our results, use of nintedanib was associated with a higher number of acute exacerbation events being avoided compared to the reference scenario (Table 4). More specifically, acute exacerbation events following the introduction of nintedanib were reduced by 18 events over the 5-year study period compared to the reference scenario.

DISCUSSION

IPF is a debilitating chronic disease with a high mortality rate. Nintedanib is a novel treatment option that offers significant clinical benefits to the patients with IPF (Fala, 2015). Management of IPF poses a substantial economic burden on healthcare systems. Resources spent on managing IPF should be yielding optimal return. This is especially critical in countries faced with the persistent challenge of an economic crisis. This is the first study to assess the impact on the budget of EOPYY of reimbursing a new therapy for the treatment of IPF in Greece.

The budget impact of reimbursing nintedanib as part of already available treatment options (pirfenidone and BSC) increasing from approximately €1.5 million in 2018 to €2.5 million in 2022, which corresponds to a maximum of 0.13% of annual total pharmaceutical expenditure. Therefore, reimbursement of nintedanib has a relatively low impact on the budget of EOPYY. Furthermore, the model estimated that a significant number of acute exacerbation events would be averted during the study period when on treatment with the new scenario versus the current scenario, thus providing additional cost savings to the NHS – and EOPYY, which reimburses hospital care for its insured population.

This is the first study that estimates the impact on the budget of EOPYY of reimbursing a new treatment for IPF. Our study findings may underestimate the actual savings of introducing nintedanib for the treatment of IPF, as it only assesses the economic impact of averting one type of adverse event, diarrhea. In addition, other studies (Yanni et al., 2016) have suggested that the majority of patients experiencing acute exacerbation are treated in outpatient settings, an assumption that has been deemed less valid in our setting by our expert and thus excluded from the analysis. The use of a DRG for calculating the cost of an acute exacerbation event may be arbitrary, as it excludes potential comorbidities that would be managed and charged under a different (additional) DRG. In actual fact, evidence suggests that more than 60% of patients with IPF have between 1 and 3 co-morbidities such as arterial hypertension, diastolic dysfunction and diabetes (Kreuter et al., 2016). Such data could not be validated on the basis of a model scenario or through an expert consultation and would require real-life patient data (such as from a disease registry or observational study) to fully capture, correctly assess and report on the impact of comorbidities on overall acute exacerbation cost and the savings to the NHS and social insurance by averting such events.

CONCLUSION

The management of patients with IPF remains a significant challenge in respiratory medicine. Nintedanib is an innovative therapy for the treatment of IPF, the reimbursement of which has a relative low impact on EOPYY budget, whilst saving healthcare resources related to management of acute exacerbation events for the Greek NHS. Data from a real-world patient registry

<table>
<thead>
<tr>
<th>TABLE 4. Reduction in acute exacerbation events following reimbursement of nintedanib, 2018-2022</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of IPF Patients per year, 2018-2022</strong></td>
</tr>
<tr>
<td>Current scenario</td>
</tr>
<tr>
<td>New scenario</td>
</tr>
<tr>
<td><strong>Acute exacerbation events per year, 2018-2022</strong></td>
</tr>
<tr>
<td>Current scenario</td>
</tr>
<tr>
<td>New scenario</td>
</tr>
<tr>
<td><strong>Acute exacerbation events averted</strong></td>
</tr>
<tr>
<td><strong>Cost of managing acute exacerbation events (averted)</strong></td>
</tr>
<tr>
<td>2018</td>
</tr>
<tr>
<td>Current scenario</td>
</tr>
<tr>
<td>New scenario</td>
</tr>
<tr>
<td>Current scenario</td>
</tr>
<tr>
<td>New scenario</td>
</tr>
<tr>
<td>Current scenario</td>
</tr>
<tr>
<td>New scenario</td>
</tr>
</tbody>
</table>
would allow a more accurate representation of both clinical benefit and resource use associated with either nintedanib or pirfenidone and BSC, and provide evidence based knowledge on the impact of such decision making on the budget of EOPYY.

FUNDING
This paper was not funded.

DECLARATION OF INTEREST
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

REFERENCES


Quality of Life after endobronchial intervention of malignant central airway obstruction

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SUMMARY

BACKGROUND: Patients with malignant central airway obstruction (mCAO) may need endobronchial intervention for symptoms relief (dyspnea, hemoptysis, post-obstructive pneumonia), but also to manage atelectasis and consequent respiratory failure that does not allow their treatment to continue. Quality of life (QoL) has been closely linked with symptom intensity in lung cancer patients. It is therefore important to relieve respiratory distress and inform patients, especially those who receive palliative care, about the benefits of an eventual endobronchial intervention. METHODS: Over an 18-month period, we enrolled 29 patients with symptomatic malignant central airway obstruction in order to re-establish airway patency. QoL and dyspnea were evaluated by the EORTC -C30 and EORTC -LC13 Questionnaire before the intervention, 1 week after and every following month until first relapse or death. RESULTS: Overall, 44.8% of patients (n=13) had poor Performance status (PS ≥3) and 51.7% (n=15) of patients were stage IV disease. QoL improved significantly from the first week up to the 6th month (p<0.05). Global Health Questionnaire improved from 29.6 (Standard deviation=19.2) to 70.8 (SD=30.5) (p<0.05) on week 24. Dyspnea accessed with EORTC-LC13 questionnaire decreased from 73.2 (SD=29.2) to 23.6 (SD=26) (p<0.05) on week 24. Patients with PS ≥3 and those at stage IV had greater improvement. Benefits were seen independent of histology of malignancy or history of post-obstructive pneumonia. Mean time until first relapse was 21.2 weeks (SD=20.5) (n=6 patients) and time until death was 15.1 weeks (SD=7.9) (n=16 patients). Patients treated with chemotherapy before the intervention and those with stenosis of trachea and left main bronchus had worse survival. CONCLUSIONS: Interventional management of patients with mCAO results in sustained significant improvement of QoL and shortness of breath and should be considered as essential component of multidisciplinary cancer care approach.

BACKGROUND

It has been estimated that 30% of lung cancer patients develop dyspnea due to malignant central airway obstruction (mCAO) and its complications.\(^1,2\) In these cases, interventional therapeutic bronchoscopy remains an important method for airway management. Symptoms like dyspnea, hemoptysis and complications like obstructive pneumonia and atelectasis deteriorate patient’s QoL and survival. Due to respiratory failure and sepsis patients who remain untreated are poor candidates for combined chemo-radio therapy. As a result, they report worse survival which commonly ranges from 1-2 months.\(^3\)

In most cases endoscopic treatment has palliative effects since about 80% of patients are not candidates for radical surgical treatment. It is therefore important that every intervention improves QoL, dyspnea and physical performance and does not merely prolong patient’s suffering.

Prior studies of therapeutic bronchoscopy for mCAO have shown statistically significant improvement of dyspnea the first month after intervention.\(^5-8,14,17\) Moreover, there is a positive impact on spirometry measurements like FEV\(_1\).\(^11,14,17\) However, only one study shows sustained benefit on QoL over 2 months after the intervention.\(^6\)

Endoscopic management of mCAO does not only have an impact on QoL but also on individual’s survival.\(^6,15,16\) A brief review of the literature reveals that patients with mCAO treated endoscopically and with combined chemo-radio therapy had the same survival as patients of the same stage but without mCAO when treated with combined chemo-radio therapy.\(^15,16\) On the contrary, patients who remained untreated for mCAO survived only 1-2 months.\(^2\) According to Stratakis Gr. et al. study, patients who denied endobronchial management had 2,93 times less likelihood of survival.\(^6\)

We aimed to study the improvement of the overall QoL and of symptoms like dyspnea in a new well-defined population with patients of different stages of lung cancer, in order to review the efficacy of the interventional management of the central airways and to identify prognostic factors of better or worse outcome.

METHODS

The goal of this prospective study was to assess the effect of therapeutic bronchoscopic interventions when added to the standard oncologic treatment in patients with mCAO. The study was performed at “Sotiria” Athens Chest Diseases Hospital after approval of the hospital’s ethical committee. Patients were enrolled over a period of 12 months while the total follow up time was 18 months. Primary objectives included assessment of QoL and dyspnea before and after endoscopic intervention. Secondary objectives were time until first relapse, survival and identification of clinical, demographic and endoscopic characteristics that affect the outcome.

Subjects

All patients referred for interventional bronchoscopy were diagnosed with endobronchial obstruction due to primary lung cancer or metastatic cancer. Central airway obstruction was defined as occlusion of >50% of the trachea or main bronchus. Patients with poor performance status and low life expectancy were also included in the study. Patients with severe cardiopulmonary compromise and bleeding disorders were excluded. All patients signed consent form before enrollment.

Interventional Bronchoscopic procedures

The endoscopic team could choose the most appropriate method to reestablish airway patency based on each case using combination of different techniques when required. The procedure could include flexible or rigid bronchoscopy combined with electro-cryotherapy, mechanical debulking, Argon Plasma Coagulation and metal or silicon stent placement. Technical success was defined as reopening of the airway lumen to >50% of normal diameter.

Quality of Life assessment

QoL was assessed using a 30-point core questionnaire designed by the European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire for Cancer (EORTC QLQ-C30, version 3) combined with the lung cancer specific module (LC-13). Dyspnea was assessed with both questionnaires EORTC QLQ-C30 and LC-13. All patients were evaluated before the intervention, 1 week after and every following month until first relapse or death.

The EORTC QLQ-C30 and LC13 are the most frequently used and well documented questionnaires in European countries\(^10,12\). They have been used and validated in over 3000 studies globally.\(^9\) QLC-C30 is composed of multi-item scales: 2 global QoL scales (Global Health Status score-GHS), 5 functioning scales (physical, role, emotional, cognitive, and social), and 3 symptom scales
(fatigue, pain, and nausea/vomiting). For the 5 functioning scales and the global QoL scale, a higher score represents better functioning. For the symptom scales and items, a higher score corresponds to a higher level of symptoms.

**Statistical Analysis**

The effect of variables recorded before endoscopy on the time of death / relapse, was quantified by a survival analysis model. Single and multivariate analysis was performed both for the time of death and for selected physical / mental health items of the questionnaire. Analysis used a 5% significance level and was performed using the R statistical packet for Windows (version 3.5.0).

**RESULTS**

During the 18-month period of the study 29 patients were enrolled. The intervention was considered successful in all patients as >50% of airway patency was achieved. Overall, 75.9% (n=22) of patients had primary lung cancer and 17.2% (n=5) had extrathoracic malignancy with endobronchial metastasis. The most frequent occlusion site was the right main bronchus in 58.6% (n = 17) of cases, followed by the trachea in 41.4% of the participants (n = 12), and the left main bronchus in 34.5% of the patients (n = 10). The majority of the patients had obstruction in more than one site (62.1%). Stent placement was reported in 12 patients (41.4%).

Almost half of the patients (44.8%, n = 13) had PS ≥3 and half of them (51.7%, n = 15) had stage IV of disease. Moreover, 58.6% of patients (n = 17) were already treated with chemotherapy and 34.5% (n = 10) with radiotherapy. A combination of radio-chemotherapy was reported in 31% of the participants (n = 9), while 20.7% (n = 6) of them had no prior treatment. (Table 1)

Most QoL data improved significantly from the first week up to the 6th month after the intervention (p<0.05) (Table 2). The Global Health Status (GHS) score improved from the initial score of 29.6 (SD = 19.2) to 70.8 (SD=30.5) on week 24 (p<0.005) (Figure 1).

Dyspnea estimated with the EORTC-LC13 questionnaire was reduced from 73.2 (SD = 29.2) to 23.6 (SD = 26) on week 24 (p<0.005) (Figure 2). Patients with PS ≥3 and those at Stage IV had worse scores before the intervention but showed the greatest improvement from the first month of follow up. The assumption that patients at advanced stage or poor PS do not benefit as much as lower-stage patients was not confirmed. The improvement was inde-

### TABLE 1 Baseline characteristics of the patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M)</td>
<td>21 (72.4)</td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (10.3)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (31.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (13.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 (27.6)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>29.0</td>
<td>62.9 (SD=9.6)</td>
</tr>
<tr>
<td>Istitology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Lung Cancer</td>
<td>22 (75.9)</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>5 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Lung Cancer pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC squamous</td>
<td>12 (54.5)</td>
<td></td>
</tr>
<tr>
<td>NSCLC adenocarcinoma</td>
<td>8 (36.4)</td>
<td></td>
</tr>
<tr>
<td>SCLC</td>
<td>1 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Position</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachea</td>
<td>12 (41.4)</td>
<td></td>
</tr>
<tr>
<td>Right main bronchus</td>
<td>17 (58.6)</td>
<td></td>
</tr>
<tr>
<td>Left main bronchus</td>
<td>10 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Stent</td>
<td>12 (41.4)</td>
<td></td>
</tr>
<tr>
<td>Positions of obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (37.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14 (48.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Stage (TNM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>15 (51.7)</td>
<td></td>
</tr>
<tr>
<td>III B</td>
<td>8 (27.6)</td>
<td></td>
</tr>
<tr>
<td>III A</td>
<td>4 (13.8)</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>1 (3.4)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>1 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Postobstructive pneumonia</td>
<td>15 (51.7)</td>
<td></td>
</tr>
<tr>
<td>ChemoTherapy</td>
<td>17 (58.6)</td>
<td></td>
</tr>
<tr>
<td>Xray Therapy</td>
<td>10 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Oxygen Therapy</td>
<td>12 (41.4)</td>
<td></td>
</tr>
<tr>
<td>Chemo &amp; Xray</td>
<td>9 (31.0)</td>
<td></td>
</tr>
<tr>
<td>Therapy Count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (20.7)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (37.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8 (27.6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Smoking PY</td>
<td>29.0</td>
<td>61.2 (SD=44.4)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>15 (51.7)</td>
<td></td>
</tr>
<tr>
<td>Coronary disease</td>
<td>2 (6.9)</td>
<td></td>
</tr>
<tr>
<td>No COPD/Coronary Disease/RenalFailure</td>
<td>12 (41.4)</td>
<td></td>
</tr>
</tbody>
</table>

- Positions of obstruction: Concurrent obstruction sites in Trachea, Right main bronchus, Left main bronchus
- Number of therapies that preceded: Chemotherapy, Radiotherapy, Oxygen Therapy.
TABLE 2. Quality of Life (EORTC Q30 & LC13) prior to intervention and follow-up from 1st week and then every month up to 6th month.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>before (n=29)</th>
<th>1 wk (n=28)</th>
<th>4 wks (n=26)</th>
<th>8 wks (n=21)</th>
<th>12 wks (n=20)</th>
<th>16 wks (n=11)</th>
<th>20 wks (n=10)</th>
<th>24 wks (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Health status</td>
<td>29.61±14.3*</td>
<td>65.1±16.8*</td>
<td>67.9±16.8*</td>
<td>67.1±17.2*</td>
<td>71.21±16.8*</td>
<td>70.01±18.9*</td>
<td>70.8±30.5*</td>
<td></td>
</tr>
<tr>
<td>Functional - Physical</td>
<td>58.81±24.1*</td>
<td>65.1±25*</td>
<td>65.41±23*</td>
<td>67.01±26.4*</td>
<td>63.6±31.6*</td>
<td>68.0±33.5*</td>
<td>70.8±35.8*</td>
<td></td>
</tr>
<tr>
<td>Functional - Role</td>
<td>44.61±28.7*</td>
<td>56.4+32*</td>
<td>55.61±29.5*</td>
<td>62.51±32.8*</td>
<td>53.0+40*</td>
<td>61.7±41.6*</td>
<td>68.8±39.3*</td>
<td></td>
</tr>
<tr>
<td>Functional - Emotional</td>
<td>75.91±22.4*</td>
<td>77.2+23.9*</td>
<td>78.21±22.3*</td>
<td>85.41±16.2*</td>
<td>83.3±13.9</td>
<td>88.3±10.5</td>
<td>89.6±8.6*</td>
<td></td>
</tr>
<tr>
<td>Functional - Cognitive</td>
<td>70.1.1±30.8</td>
<td>80.1±21.6*</td>
<td>80.21±19.5</td>
<td>84.2±17.5</td>
<td>89.4±15.4</td>
<td>91.7±114.2</td>
<td>89.6±15.3*</td>
<td></td>
</tr>
<tr>
<td>Functional - Social</td>
<td>37.9±30.8</td>
<td>57.71±26.2*</td>
<td>62.8±26.4*</td>
<td>61.91±28.4*</td>
<td>69.21±19.7*</td>
<td>68.2±24.1*</td>
<td>75.0±118.7</td>
<td>79.21±17.3</td>
</tr>
<tr>
<td>Symptom - Fatigue</td>
<td>72.01±29.5</td>
<td>42.51±24.8*</td>
<td>39.71±26.9*</td>
<td>42.9+24.7*</td>
<td>35.61±19.3</td>
<td>37.41±21.2*</td>
<td>30.01±18.9*</td>
<td>31.91±28.8</td>
</tr>
<tr>
<td>Symptom - Nausea &amp; Vomiting</td>
<td>12.11±17.2</td>
<td>3.01±19.1*</td>
<td>5.8±16.3*</td>
<td>7.9±19.5*</td>
<td>5.8+12.4*</td>
<td>4.5+10.8*</td>
<td>0.0+0</td>
<td>0.01±0</td>
</tr>
<tr>
<td>Symptom - Pain</td>
<td>39.1±40.2</td>
<td>24.4+29.2*</td>
<td>25.01±30.6*</td>
<td>26.2+31*</td>
<td>18.3+21.6*</td>
<td>13.6+22.1*</td>
<td>8.3+14.2*</td>
<td>12.51±14.8</td>
</tr>
<tr>
<td>LC13 - Dyspnoea</td>
<td>73.2±29.2</td>
<td>38.1+19.7*</td>
<td>32.11±23.8*</td>
<td>32.31±20.8*</td>
<td>30.01±24.7*</td>
<td>26.31±22.4*</td>
<td>25.6+29.2*</td>
<td>23.61±26.2*</td>
</tr>
<tr>
<td>LC13 - Haemoptysis</td>
<td>39.1±41.9</td>
<td>9.51±15.3*</td>
<td>5.11±20.4*</td>
<td>0.01±0*</td>
<td>1.71±7.5*</td>
<td>0.0+0</td>
<td>0.0+0</td>
<td>4.2+11.8</td>
</tr>
<tr>
<td>LC13 - Coughing</td>
<td>77.0±28.3</td>
<td>35.7±12.6*</td>
<td>32.11±27.5*</td>
<td>31.71±22.3*</td>
<td>31.71±25.3*</td>
<td>27.31±29.1*</td>
<td>23.31±27.4*</td>
<td>20.81±24.8*</td>
</tr>
</tbody>
</table>

*Values differ statistically significantly compared to pre-bronchoscopy values.

FIGURE 1. Global Health Status Questionnaire: Before invasive bronchoscopy and follow-up at 1st week and then every month until 6th month.

The mean follow-up time was 22.5 weeks (SD 9.6, median = 17, min = 0.1, max = 70 weeks). Overall, 16 patients died, 6 relapsed and new intervention was needed, 6 patients did not relapse until the study was completed, and one was missed during follow-up on 5th month. The mean time until first relapse was 21 weeks (mean = 21.2 weeks, SD = 20.5), suggesting that for 5 months patients who suffocated or were at risk of infections had adequate time to receive the proper oncology treatment with improved daily QoL. Moreover, the median survival time was 3.5 months (mean = 15.1 weeks, SD = 7.9), longer than the expected 1-2 months survival in not interventionally
treated patients according to the older study by Macha et al (Table 3).

Regarding the complications of invasive bronchoscopy, endobronchial bleeding occurred in one patient and was controlled with a new bronchoscopy the first 48 hours after intervention. Also, one patient with stent presented with MRSA pneumonia 6 months after the intervention and the stent was removed.

Since there is no control group to compare the time of relapse or death, an analysis of the patient characteristics that could affect that time was performed. Univariate analysis demonstrated that patients with PS ≥3 and those already treated with chemotherapy had worse survival at 6 months. However, in the multivariate analysis, when all the features were studied simultaneously, PS was no more considered as a negative predictive factor (Table 4).

Analysis showed that tracheal obstruction increased the risk of death by 12.93 times (p < 0.05) (Figure 3). In addition, left main bronchus obstruction increased the risk of death by 7.65 times (p < 0.05) and the combination of tracheal and left main bronchus stenosis had the worst prognosis (Figures 4 and 5). A possible explanation could be that trachea obstructions are more critical for breathing impairment since trachea is the central airway

### Table 3. Follow up and outcome (weeks).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>16 (55.2)</td>
</tr>
<tr>
<td>Relapse</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Without relapse*</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (3.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up Weeks</th>
<th>N(%)</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>29.0</td>
<td>22.5</td>
<td>17.1</td>
<td>17.0</td>
<td>0.1</td>
<td>70.0</td>
</tr>
<tr>
<td>Weeks to Death or Relapse</td>
<td>22.0</td>
<td>16.7</td>
<td>12.4</td>
<td>16.5</td>
<td>0.1</td>
<td>60.0</td>
</tr>
<tr>
<td>Weeks to death</td>
<td>16.0</td>
<td>15.1</td>
<td>7.9</td>
<td>16.5</td>
<td>0.1</td>
<td>30.0</td>
</tr>
<tr>
<td>Weeks to relapse</td>
<td>6.0</td>
<td>21.2</td>
<td>20.5</td>
<td>15.0</td>
<td>4.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Without relapse or lost follow up*</td>
<td>7.0</td>
<td>40.7</td>
<td>17.7</td>
<td>43.0</td>
<td>17.0</td>
<td>70.0</td>
</tr>
</tbody>
</table>

* Follow up of patients without relapse stopped due to completion of study time
and even slightest stenosis may have a significant effect on the oxygenation. Furthermore, interventions in the left main bronchus are technically more demanding according to Ost et al. Finally, the history of previous chemotherapy reduced survival by 4.49 times (p < 0.05) (Figure 6). Regarding the patients already treated with chemotherapy, it is likely that their tumor was more resistant to size reduction. On the contrary, treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea</td>
<td>12.93</td>
<td>2.94-56.81</td>
<td>0.1%</td>
</tr>
<tr>
<td>Left main bronchus</td>
<td>7.65</td>
<td>2.14-27.28</td>
<td>0.2%</td>
</tr>
<tr>
<td>Chemo therapy</td>
<td>4.49</td>
<td>1.18-17.15</td>
<td>2.8%</td>
</tr>
<tr>
<td>Smoking PY</td>
<td>1.01</td>
<td>1.00-1.03</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

* Conclusions should be carefully evaluated after 6 months (24 weeks) as the sample is small. The survival curves display data beyond 6 months.

**FIGURE 3.** Multivariate analysis: Survival of patients with tracheal obstruction compared to those who did not have tracheal obstruction (had only occlusion in the main bronchus).

**FIGURE 4.** Multivariate analysis: Survival of patients with left main bronchus obstruction.
 naïve patients benefited from both the central airway opening and the additional effect of chemotherapy ± radiotherapy. A similar result was reported by Kyeongman from a 5 years retrospective study.19 The stage of disease or the history of post-obstructive pneumonia were not found to affect the outcome.

This study has several limitations. First of all, it is a single reference center study and the cohort of patients (n = 29) is small, so extrapolation of the results to larger number of patients and bronchoscopic centers, is not safe. Another limitation is the coexistence of patients with primary and metastatic extrathoracic lung cancer as the course of the disease is expected to differ. However, according to Mahmood et al. study, survival between the two groups was not affected.17 Moreover, the overall monitoring time was limited due to the initial study design and the statistical analysis included data from a 6-month follow-up. It is difficult to understand whether the improvement observed was only because of the endoscopic intervention or whether it was influenced by other types of concomitant therapy. Time was given though for chemotherapy and radiotherapy to work and

FIGURE 5. Multivariate analysis. Impact of obstruction site on survival. The combination of obstruction in the trachea and left main bronchus has the worst outcome in the follow-up period. Note: none = occlusion in the right main bronchus only.

FIGURE 6. Multivariate analysis: Survival of patients who received chemotherapy before study enrollment.
protect patients from complications such as suffocation, pneumonia and sepsis that are not necessarily related to the stage of the disease. Due to ethical reasons, no control group was included in our study as bronchoscopic intervention could not be denied to any patient with mCAO, thus no comparison could be made.

CONCLUSIONS

In this prospective study, we found a positive impact of therapeutic bronchoscopy on QoL and dyspnea scale values in patients with mCAO. This improvement was observed regardless of the type of malignancy causing the airway obstruction. Scores were significantly improved from the first week and remained so throughout the 6-month follow-up period. As the deterioration of respiratory symptoms is associated with worse QoL, decreased physical activity, reduced self-care ability and a significant reduction in social activities regardless of stage \textsuperscript{18}, the emergence of this improvement has a significant impact on patient’s decision to undergo an invasive procedure. The disease stage and poor PS, especially when this is attributed to dyspnea, should not exclude patients from endoscopic intervention. Finally, although there was no control group, there is evidence that survival time is prolonged, as has been shown by other studies \textsuperscript{3,6}, but this should be carefully assessed. Multi-center studies with larger number of patients and longer follow-up period are needed.

It is important to recognize the necessity of invasive bronchoscopy and to ensure that specialized hospitals where complicated cases of lung cancer are treated and all large oncology units are familiar and have access to interventional endoscopic procedures. Interventional management of patients with mCAO results in sustained significant improvement of QoL and shortness of breath and should be considered as an essential component of the personalized multidisciplinary oncology care approach.

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DECLARATION OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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ΠΕΡΙΛΗΨΗ

Ποιότητα ζωής σε ασθενείς με καρκίνο πνεύμονα μετά τη διάνοιξη κεντρικών αεραγωγών

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Εισαγωγή: Οι ασθενείς με κακοήθη απόφραξη κεντρικού αεραγωγού έχουν ένδειξη επεμβατικής διάνοι-ξης για τη βελτίωση των συμπτωμάτων τους (δύσπνοια, αιμόπτυση, μεταποφρακτική πνευμονία) αλλά και για την ύπαρξη ατελεκτασιών και συνεπακόλουθης αναπνευστικής ανεπάρκειας που δεν επιτρέπει τη συνέχιση της θεραπείας τους. \textbf{Μέθοδοι:} Κατά τη διάρκεια 18 μηνών εντάχθηκαν στη μελέτη 29 ασθενείς, οι οποίοι αντιμετωπίστηκαν με επεμβατική βρογχοσκόπηση για διάνοιξη κακοήθους απόφραξης κεντρικού αεραγωγού. Η ποιότητα ζωής και η δύσπνοια αξιολογήθηκαν με τα προτυποποιημένα ερωτηματολόγια EORTC-C30 και EORTC-LC13 πριν την παρέμβαση, 1 εβδομάδα μετά και έπειτα κάθε μήνα μέχρι την πρώτη υποτροπή ή τον θάνατο. \textbf{Αποτελέσματα:} Το 44.8% των ασθενών (n=13) είχαν φτωχό Performance status
(PS) (≥3) και το 51.7% (n=15) των ασθενών βρισκόταν στο IV στάδιο της νόσου. Η ποιότητα ζωής βελτιώθηκε στατιστικά σημαντικά από την πρώτη εβδομάδα παρακολούθησης και καθ’ όλη τη διάρκεια του επόμενου 6μηνου. Το ερωτηματολόγιο Global Health Questionnaire βελτιώθηκε από 29.6 (SD=19.2) σε 70.8 (SD=30.5) (p<0.05) την 24η εβδομάδα. Η δύσπνοια (εκτιμώμενη με το EORTC-LC13) μειώθηκε από 73.2 (SD=29.2) στο 23.6 (SD=26) (p<0.05) την 24η εβδομάδα. Οι ασθενείς με PS ≥3 και αυτοί σταδίου IV είχαν τη μεγαλύτερη βελτίωση. Ο μέσος χρόνος μέχρι την πρώτη υποτροπή ήταν 21.2 εβδομάδες (SD=20.5) (n=6 ασθενείς) και ο μέσος χρόνος μέχρι το θάνατο ήταν 15.1 εβδομάδες (SD=7.9) (n=16 ασθενείς). Οι ασθενείς με προηγηθείσα χημειοθεραπεία και όσοι είχαν απόφραξη στην τραχεία και τον αριστερό στελεχιαίο βρόγχο είχαν χειρότερη πρόγνωση.

Συμπέρασμα: Η επεμβατική διάνοιξη σε ασθενείς με κακοήθη απόφραξη κεντρικού αεραγωγού βελτιώνει σημαντικά και σταθερά την ποιότητα ζωής και τη δύσπνοια και θα πρέπει να αποτελεί μέρος της σύγχρονης διατομεακής ογκολογικής αντιμετώπισης.

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Systemic Sclerosis - Associated Pulmonary Hypertension

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Key words:
- Pulmonary hypertension
- Scleroderma

SUMMARY
Lung disease is a major complication of systemic sclerosis associated with high morbidity and mortality rates. Pulmonary hypertension and lung fibrosis are the prevalent manifestations of lung disease, usually with overlapping characteristics. A major challenge in the management of the disease, is to identify the phenotypes of patients who might benefit from specific therapeutic modalities. The aim of the present review is to describe the clinical and epidemiological characteristics, classification, risk assessment and management of systemic sclerosis associated pulmonary hypertension. Pneumon 2018, 31(4):223-230.

INTRODUCTION
Systemic Sclerosis (SSc) is characterized by inflammation, fibrosis and diffuse vasculopathy, caused by an autoimmune mechanism, triggered by environmental stimulus in genetically susceptible persons. The fibrotic manifestations of SSc are provoked by fibroblast proliferation, stimulated by transforming growth factor (TGF)-β, tumor necrosis factor-α, platelet-derived growth factor and fibronectin, which are produced by macrophage activation. Vascular endothelial growth factor is increased as well, leading to neoangiogenesis. The fibrotic process and the neoangiogenesis contribute to SSc lung disease, characterized by lung fibrosis, nonspecific interstitial pneumonia and pulmonary vasculopathy. Smooth muscles hypertrophy and proliferation of adventitia and intima with in situ thrombosis and plexiform lesions result in elevated pulmonary vascular resistance and subsequent pulmonary hypertension (PH).

Pulmonary hypertension (PH) is a severe complication of SSc, and a main cause of mortality, despite the widespread use of targeted therapies. The definition of PH is based on elevated mean pulmonary artery pressure \( \geq 25 \) mmHg, assessed by right heart catheterization, while precapillary PH is characterized by pulmonary artery wedge pressure \( \leq 15 \) mmHg. The prevalence of PH in SSc patients is more than 10%, while it may be caused in the setting of group 1 (pulmonary arterial hypertension-PAH), group 1'...
(pulmonary veno-occlusive disease-PVOD/pulmonary capillary hemangiomatosis), group 2 (PH due to left heart disease), group 3 (PH caused by chronic lung disease) or group 4 (chronic thromboembolic PH)⁷. In this review, we will describe the current knowledge on clinical characteristics, diagnostic and screening issues, risk stratification, prognosis and treatment options in SSc - associated PH.

**PREVALENCE AND RISK FACTORS**

PAH is a significant cause of morbidity and mortality in SSc patients. Interestingly, according to a US study of causes of death in SSc patients, scleroderma renal crisis has been substituted by pulmonary fibrosis and PAH, as the commonest cause of death⁸. Additionally, the presence of PAH in SSc patients is associated with higher mortality compared to SSc patients without PAH⁹. Moreover, connective tissue disease – associated PAH is characterized by poorer survival rates compared to idiopathic PAH (IPAH)¹⁰, whereas patients with SSc-associated PAH experience higher mortality compared to patients with IPAH¹¹. SSc – associated PAH carries poorer survival rates compared to non-SSc CTD – PAH subgroups, including systemic lupus erythematous and mixed connective tissue disease. This was confirmed by the REVEAL registry (Registry to Evaluate Early and Long-term PAH Disease Management), showing that the 3-year survival in patients with SSc-PAH was lower, as compared to non-SSc CTD-PAH patients¹⁰.

The incidence of PAH in SSc ranges between 5 and 12% depending on the study⁶. As it has been indicated in the PHAROS cohort (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma), PH developed in 10% of SSc patients after 2 years of attendance, 13% after 5 years and 25% after 5 years¹². The incidence rate is estimated to 1-2% per year¹³.

Risk factors for the development of PH in SSc are older age, late onset of the disease post-menopausal status and limited cutaneous type of the disease¹⁴. Moreover, the risk of PAH is higher in SSc patients, who show evidence of other aberrant vascular phenomena, like telangiectasias¹⁵.

There are also several parameters measured in pulmonary function tests, which are associated to the development of PH: low DLCO (<50% of predicted), DCO/alveolar volume less than 70% and FVC%/DLCO% ratio >1.6)¹⁶. Regarding the autoantibodies, the presence of anticentromere antibodies, nucleolar pattern of antinuclear antibodies (ANA), anti-U1-ribonucleoprotein (RNP), antiphospholipic antibodies against cardiolipin and beta2-glycoprotein 1 and the lack of anti-Scl-70, are risk factors for development of PAH in SSc patients¹⁷.

**DIAGNOSIS**

Diagnosis of PAH is established by right heart catheterization (RHC). There are several screening approaches to identify SSc patients who should be early referred for RHC. According to ESC/ERS 2015 guidelines, patients should be referred for RHC if echocardiography reveals: triscupid regurgitant velocity (TVR) >3.4 m/sec, or TVR >2.8 ≤3.4 m/sec and current dyspnea, current syncope/near syncope, peripheral edema, or TVR ≤2.8 m/sec and additional suggestive echo variable⁵. Another screening algorithm is proposed by Australian Scleroderma Interest Group, including N-terminal pro b-type natriuretic peptide (NT-proBNP) and pulmonary function tests (PFTs)¹⁸ (Fig. 1). Moreover, the DETECT algorithm integrates non-invasive

![FIGURE 1. ASIG screening algorithm. ASIG: Australian scleroderma Interest Group, DLCO: Diffusing capacity for carbon monoxide, FVC: Forced vital capacity, RHC: Right heart catheterization.](image-url)
clinical and laboratory parameters and echocardiography, in order to assess the risk of PH\(^1\) (Fig 2). As a first step, six variables are recorded (FVC, telangiectasia, anticentromere antibody positivity, ECG right access deviation and serum levels of NT-proBNP and urate). Since the subsequent score surpasses a threshold, ECG parameters are calculated, and a new score is assessed. RHC is recommended if the risk of development of PH is considered high. DETECT algorithm has shown high sensitivity and negative predictive value\(^2\). However, it was derived from a cohort of patients with SSc duration of >3 years and predicted diffusing capacity for carbon monoxide (DLCO) <60%. In general, ECG, NT-proBNP levels, PFTs and clinical assessment, are useful for predicting the risk of development of PAH.

CLASSIFICATION

According to the ERS/ESC guidelines, PH is divided in 5 categories. The most common category of PH, observed in more than 50% of SSc patients with PH, is PAH (group I). There are histological similarities between SSc-associated PAH and idiopathic PAH, characterized by thickening of media and muscularization of arterioles, while plexiform lesions are less common\(^2\). Moreover, SSc-associated PAH might also present overt signs of venous and capillary involvement, in the context of pulmonary veno-occlusive disease (PVOD), which is classified as Group I’ PAH. There are also SSc patients with post-capillary PH due to cardiac involvement (group II) or PH caused by interstitial lung disease (ILD) and hypoxia (group III)\(^1\). The extent of lung fibrosis is determined by computer tomography (CT) assessment and by FVC values. Lung fibrosis might be considered as a cause of PH, if it affects more than 20% of the lung volume, in high resolution CT (HRCT) imaging. Moreover, FVC <70% is consistent with extensive fibrosis\(^2\). Thrombosis might also be present in SSc patients implicating the development of chronic thromboembolic pulmonary hypertension (CTEPH), the Group IV of PH classification.

The classification of SSc patients in a certain PH group is challenging, as there are mixed phenotypes with overlapping clinical characteristics and different response to therapy. Moreover, in the same patient, clinical classification of PH may change during the course of the disease. In the prospective observational PHAROS cohort, it was shown that the pulmonary artery wedge pressure (PAWP) in SSc patients with PH could significantly change on follow up RHC\(^2\). These changes are meaningful as they affect the classification and the subsequent therapeutic choices. The increase of PAWP over time might be attributed to

FIGURE 2. DETECT screening algorithm.
the development of heart failure with preserved ejection fraction (HFpEF)\textsuperscript{24}. Moreover, the specific PH therapy and diuretics can alter right ventricular (RV) function and left ventricle (LV) filling pressures, by ventricular interdependence\textsuperscript{25}. Helpful procedures to recognize group II PH are the fluid challenge and exercise test during RHC.

Therefore, PH in SSc patients can be precapillary or postcapillary, while the classification might change over time. However, SSc patients with precapillary PH form an heterogeneous group, in which the predominant mechanism of PH might be the parenchymal lung involvement or the vascular disease. Several patients present with clinical and pathological characteristics lying between these two extremes. In order to identify different phenotypes of precapillary PH in SSc, Launey et al performed a cluster analysis\textsuperscript{26}. According to lung function tests, hemodynamic and radiological data, patients were classified to four clusters characterized by a different extent of PAH, ILD and DLCO. The worst prognosis was observed in patients with extensive ILD irrespectively of the hemodynamic values. The prognosis was also poor in patients with severe PAH with mild ILD and low DLCO, in whom hemodynamic parameters played a prognostic role. Therefore the classification of PH in SSc patients is important for the clinician, to identify the underline pathological mechanism of the disease, to define the future risk and to take therapeutic decisions.

**DISEASE PROGRESSION**

The DETECT study developed an algorithm aiming to identify SSc patients with high suspicion of PH, who should be referred for RHC, in order to be diagnosed earlier. As the prognosis of the milder stage of the disease was not clearly defined, 88 patients enrolled in the DETECT study, were longitudinally observed on a yearly basis, to identify parameters associated with a worse outcome. The study showed that 43.9% of patients with PAH developed a disease progression, while 16% of them died during the follow up period. The 1-year survival rate was 93%. Interestingly, most of these patients were on WHO FC I or II with mean PAP 29mmHg and PVR 270 dynes. Therefore, the development of even mild PAH might be a severe complication of SSc conferring an unfavorable prognosis. Factors associated with uneventful outcome were male gender, lower DLCO\%, higher FVC%/DLCO\% and higher Borg Dyspnea Index\textsuperscript{27}.

Another subgroup of SSc patients at risk for developing severe PAH, consists of patients with mPAP 21-24 mmHg, also called borderline PAH (BoPAH). In the PHAROS cohort, 88% of BoPAH patients developed exercise-induced PH (mPAP >30mmHg) compared to 56% of patients with normal mPAP on RHC\textsuperscript{28}. Moreover, 55% of the BoPAH patients developed PH after 2 years of follow up, compared to 32% of patients with initially normal hemodynamics. A more recent study of the incidence of PH in SSc patients showed that BoPAH was present in 32.4% of the population. During the follow up period, these patients showed a significantly higher probability to develop PAH as compared to patients with normal pressures at baseline. Independent risk factors for the development of PH were PVR, tricuspid regurgitation velocity, DLCO and size of inferior vena cava\textsuperscript{29}. Moreover, patients with BoPAH showed a trend towards lower survival rate than those with normal mPAP at baseline. Therefore, BoPAH could be considered as an intermediate stage preceding the occurrence of PAH. Exercise RHC might help unmasking the group of SSc patients with BoPAH, who are more likely to develop PAH.

**RISK STRATIFICATION**

It has been shown, that PH patients with 3 or 4 low-risk risk stratification criteria included in the European PH guidelines, are characterized by better long-term outcome\textsuperscript{30}. However, the prognostic value of these criteria is not well established in SSc patients with PA. The same analysis was repeated in a large group of SSc patients with PAH, who did not show signs of significant ILD in high resolution CT. The recorded low risk criteria were: NYHA FC I or II, 6MWD >440m, right atrial pressure (RAP) <8 mmHg and cardiac index (CI) ≥2.5 lt/min/m\textsuperscript{2}. Among these parameters, baseline values of 6MWD and CI were independently associated with the outcome. However, all the low risk criteria were associated with outcomes at first follow up. In patients with 3-4, 2, 1 and no low-risk criteria, the respective three year survival rate was 84%, 73%, 45% and 35% respectively\textsuperscript{31}.

Regarding the prognostic role of follow up hemodynamics in SSc PAH patients, Weatherald et al studied the association of hemodynamic parameters with transplant-free survival. At follow up, transplant – free survival was independently associated with 6-MWD, NYHA-FC, Cardiac Index (CI), Stroke Volume Index (SVI), Pulmonary arterial compliance and Pulmonary Vascular Resistance (PVR)\textsuperscript{32}. However, at baseline, only 6MWD was an independent
predictor of survival and none of the hemodynamic parameters. Moreover, a cluster analysis of PHAROS database was performed, aiming to identify a high risk phenotype of the SSc-PAH patients. The group of patients with the highest mortality showed a decline in 6MWD at follow-up and a trend towards increased BNP values. Since the baseline measurements are insufficient to identify high risk patients, the authors suggest close follow-up and rapid titration of vasodilator therapy or referral to transplantation, in case of deterioration.

THERAPY

There are several algorithms guiding the therapeutic options in patients with SSc and ILD or PAH. Various parameters, as the extend of fibrosis in HRCT, the lung function tests and the disease duration and progression, contribute to the therapeutic decisions. Immunosuppressive medication is the most commonly used treatment option for SSc-ILD, well studied in randomized controlled trials. Cyclophosphamide is an alkylating agent, which might lead to improvement in FVC and dyspnea. Use of mycophenolate mofetil, an inhibitor of inosine monophosphate dehydrogenase, leads to a stabilization or improvement of FVC or DLCO, in SSc patients with ILD.

There are various experimental therapies for SSc-ILD targeting to molecular pathways involved in fibrosis procedure. Fresolimumab is one of these targeted therapies. It is a monoclonal antibody to transforming growth factor-beta (TGF-β), which plays an important role in fibrosis. Other antifibrotic agents approved in idiopathic pulmonary fibrosis are pirfenidone and nintedanib. Several clinical trials studying the therapeutic use of these antifibrotic agents in SSc patients are underway. Tocilizumab and Rituximab are other monoclonal antibodies that have come on interest in therapy of SSc-ILD.

PAH treatment in SSc patients aims to the improvement of functional class. In PH patients classified in Group I, all the categories of PH medications have been tried: Phosphodiesterase 5 (PDE-5) inhibitors, riociguat, endothelin receptor antagonists (ERA) and prostacyclins. IV epoprostenol improves exercise tolerance, WHO-FC and hemodynamics. Selexipag, an oral prostacyclin receptor agonist, has been studied in a subgroup of patients with connective tissue disease, in the context of GRIPHON study. The medication was well tolerated, leading to a delay of disease progression. Combination therapy with tadalafil and ambrisentan, has been studied in SSc-PAH patients, in a subgroup analysis of AMBITION study, showing improved outcomes. In the PHAROS registry, patients receiving monotherapy with an ERA alone, showed a quicker time to clinical worsening, as compared to those receiving PDE-5 inhibitors or combination PDE-5/ERA. Regarding anticoagulation, it has been shown that warfarin administration in SSc-PAH patients was associated with worse outcomes.

In SSc patients with ILD and PH there are not current treatment recommendations. A group of patients, in whom, PH is disproportionate to the degree of the underlying parenchymal disease, might benefit from specific PAH therapy. An online survey was performed in US PH treatment centres, in order to investigate the administration of PAH – directed therapy in patients with non-group 1 PH. 80% of centres participating in the survey reported the use of PAH directed therapy in group 3 of PH patients. The main parameters affecting the clinicians’ decision to give PAH specific therapy were the presence of right heart failure, poor right ventricular (RV) function and the significantly impaired pulmonary hemodynamics (mean PAP >35 mmHg). However, any vasodilator therapy should be used with caution, as it might aggravate the ventilator-perfusion rate and worsen the subsequent hypoxia. More clinical studies are necessary to identify the phenotype of SSc- associated ILD and PH, that might respond to PAH-targeted therapy. RV metrics should be included in these studies, in order to evaluate the effect of PAH – therapy on RV function.

Lung transplantation might be a therapeutic option for patients with SSc and PH/ILD. In several centres, SSc patients are not considered as candidates, as oesophageal involvement is associated with increased risk of aspiration, leading to potential graft failure. There also concerns about previous immunosuppressive and steroid therapies, which may lead to post-transplantation complications. However, observational studies have shown that patients with SSc-PAH who were transplanted, had comparable survival to transplanted patients with idiopathic PAH or idiopathic pulmonary fibrosis. Therefore, for SSc patients with end-stage lung disease, lung transplantation might be a treatment option.

CONCLUSIONS

PH is an important complication of SSc and a predominant cause of morbidity and mortality. Several screening approaches have been developed to identify high risk
patients who should early be referred for RHC. The classification of PH in SSc patients is challenging, since mixed phenotypes are usually present, with arterial, venous or capillary involvement. The prognosis of the disease is unfavourable, whereas baseline hemodynamic measurements are insufficient to identify the high risk population. Several treatment options are available, including immunosuppressives, PAH-specific therapy and transplantation. However, mortality rates remain high. Close clinical and hemodynamic monitoring of these patients and subsequent prompt administration of specific therapy or early referral for transplantation, might improve the prognosis of this devastating complication of SSc.

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Is High-frequency chest wall oscillation (HFCWO) effective in COPD patients?

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Key words:
- COPD
- HFCWO

SUMMARY

BACKGROUND The incidence of Chronic Obstructive Pulmonary Disease is increasing every year, increasing the economic burden on the healthcare system. High frequency chest wall oscillation device is another airway clearance technique that according to several studies has a positive benefit in the respiratory symptoms experienced in cystic fibrosis and bronchiectasis patients. METHODS Literature search in the Cochrane library, PubMed, Medline, PEDro SPORTDiscus, AMED, and CINAHL with the following keywords: physiotherapy, exercise, rehab, HFCWO, high frequency chest wall oscillation, positive pressure, COPD, Chronic obstructive pulmonary disease. RESULTS Four studies met the inclusion criteria. Overall, the studies showed positive results for the use of HFCWO in COPD patients of varying stages and acuteness. Only one study reported adverse effects. CONCLUSIONS HFCWO could be potentially added to the treatment of patients with COPD, however future studies need to be done using HFCWO in patients with COPD.


INTRODUCTION

Aim of the study:

The aim of this review is to describe the current and available evidence for the use of High Frequency Chest Wall Oscillation in patients with Chronic Obstructive Pulmonary Disease.

Background:

COPD:

Chronic Obstructive Pulmonary Disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a "common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar..."
abnormalities usually caused by significant exposure to noxious particles or gases. The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person” (GOLD 2017). The main cause of COPD is smoking; by inhaling the smoke and thus all the toxins, chronic lung inflammation occurs as these harmful particles become trapped in the alveoli (Kaul 2007). Chronic inflammation then causes structural changes (dysfunction and the loss of cilia in combination with the enlargement of the mucus-secreting glands), narrowing of the small airways and damage of the lung parenchyma. These result to loss of lung volume, reduction in the lung elastic recoil and increase the risk of lung collapse during expiration. In addition, COPD patients experience airflow limitation and recurrent chest infections (GOLD 2017, Kaul 2007, West 2008). The most common symptoms these patients experience include dyspnoea, chronic cough and excessive mucus production (WHO 2018). Large epidemiological studies have estimated the incidence of COPD cases to be 384 million in 2010 (global prevalence of 11.7%), with an annual mortality of approximately 3 million deaths. It is believed that there is going to be an increase in the prevalence of COPD over the next 30 years with a mortality approaching 4.5 million annually. This is thought to be due to the increase in smoking in the developing countries and the increase in the aging population in the developed countries (GOLD 2017, WHO 2018). The World Health Organisation (WHO) predicts that by 2030 COPD will become the third leading cause of death worldwide (WHO 2018). In addition to the social burden, COPD has significant economic consequences. According to GOLD (2017) the cost for COPD is approximately 38.6 billion Euros in the European Union (56% of the total cost of respiratory disease), with COPD exacerbations accounting for the biggest part of that cost. Furthermore, not all healthcare systems offer long-standing care services for these patients, especially as the disease progresses. Thus, it might lead to at least 2 people taking early retirement (the individual with COPD and their carer- who will have to look after them). This has an economic and social impact as it reduces both the family income and the human capital (GOLD 2017). **HFCWO:** Hight frequency chest wall oscillation (HFCWO) device is an airway clearance technique that was firstly used by King et al in 1983 on dogs. Currently, it is used in the mobilisation of secretions in patients with cystic fibrosis, bronchiectasis and neuromuscular disorders. It entails that the user wears an inflatable (pneumatic) vest over their thorax which is connected to an air pulse generator. The generator sends rapid pulses of air (5-20 times/second) to the vest, causing it to inflate and deflate and putting pressure on the chest walls. The changes in the pressure result in oscillatory chest wall compressions, of high velocity and low amplitude, which loosen the mucus from the airway lining and move phlegm proximally to be removed by coughing or suctioning (Goktalay et al 2013, Farag and EL-Syed 2018, Mahajan et al 2011). Further advantages of HFCWO include its use in more severe cases when the patient is unable to use a handheld device well. Also, once the carer is trained, there is limited need for a professional healthcare provider to be present at every use, this allows the patients to stay at home, increasing patient autonomy and reducing the need of hospital admissions and healthcare costs (Farag and EL-Syed 2018, Chakravorty, Chahal and Austin 2011). Typically, treatment lasts for 20 to 30 minutes with the patient stopping every 5 minutes to cough out any phlegm if needed. Initially the HFCWO device is set at a low pressure and frequency settings which are then gradually increased to the recommended values according to the patient’s tolerance. This is called the “tuning procedure” with an optimum oscillating frequency recommended between 13-15Hz (Farag and EL-Syed 2018, Mahajan et al 2011, Chakravorty, Chahal and Austin 2011, Goktalay et al 2013). Indications, contraindications and potential adverse effects of HFCWO (UTMB Respiratory Care Services 2018) can be found in Table 1. **Current Evidence:** Below, the current evidence is presented which is scarce and controversial. It mostly includes posters and studies with a mixed population sample (i.e. patients with COPD and asthma). Krishman et al (2009) and Mahajan et al (2011) compared active and sham HFCWO in 52 COPD and asthma patients, respectively. Although, both showed a high patient adherence, comfort, perceived benefit, satisfaction, change in predicted percentage of Forced expiratory volume in 1 second (FEV, % predicted) and sputum volume, only the dyspnoea score was significantly improved in HFCWO group at the end of the studies.
Diette et al\textsuperscript{12} (2007) compared active and sham HF-CWO therapy in 50 COPD patients. They showed that after 12 weeks the active group had a lower rate of acute exacerbations and lower phlegm production compared to the sham group. Also, coughing up phlegm was more likely to become easier in the active group and the quality of life improved in both groups without any significant differences. In contrast with the other two studies, self-adherence was lower in the active group.

When intrapulmonary percussive ventilation (IPV) was compared to HFCWO and control in 60 severe COPD patients, the results showed a significant improvement in the tests for dyspnoea, quality of life assessment, pulmonary function tests and Arterial Blood Gases (ABGs) in the active groups compared to the control. With in-between group comparison results favouring the IPV technique. (Russo et al\textsuperscript{13} 2014)

In Waycker et al\textsuperscript{14} (2012) retrospective pre/post cohort study, they looked at 1000 non-CF bronchiectasis and COPD patients. The results from the COPD patients only, using HFCWO, demonstrated a 40\% reduction in the mean number of all-cause hospitalisation and a significant reduction in the physician office visits and emergency department visits.

Kachel et al\textsuperscript{15} (2005) favour the long-term (90 days) use of HFCWO in 94 moderate-to severe COPD patients, who were trained to use the HFCWO at home. Improvements were seen in symptoms such as dyspnoea, 6-min walking distance (which was clinically significant) and in the role-physical domain in the quality of life questionnaire.

Lastly, Chakravorty et al\textsuperscript{16} (2011) showed that 16 COPD patients with acute exacerbations improved in terms of lung function, exercise capacity and health-related quality of life scores when discharged home using the HFCWO vest compared with conventional treatment.

Sievert and Beamer's\textsuperscript{17} (2017) study analysed the cost-effectiveness of using HFCWO (SmartVest) in 59 non-CF bronchiectasis patients and they found statistically significant results when compared to standard care (control). There was a 58\% reduction in cost due to less antibiotic use, a 63\% reduction in Accident & Emergency cost due to less attendances and a 60\% reduction in hospitalisation cost due to less admissions. Overall, the analysis of SmartVest use, showed an annual savings of $3,045 per patient per year (Sievert and Beamer 2017).

**Reasoning:**

COPD puts a heavy load to the healthcare sector every year. In view of the above evidence supporting patient benefit and cost-effectiveness, it might be useful for physicians to consider the use of HFCWO for their COPD patients.

**METHODS AND RESULTS**

A comprehensive literature search was done in the Cochrane library, PubMed, Medline, PEDro SPORTDiscus, AMED, and CINAHL with the following keywords: physiotherapy, exercise, rehab, HFCWO, high frequency chest wall oscillation, positive pressure, COPD, Chronic obstructive pulmonary disease. The titles of the articles obtained were then screened to ensure relevance. The articles whose titles lacked clarity had their abstract checked. Studies evaluated to be inappropriate to the study by their titles or abstracts were discarded. The full-text versions of the potential articles were retrieved and checked according to the criteria for this review. Studies that failed to meet the criteria were also discarded (Figure 1).

The inclusion and exclusion criteria can be found in
Table 2 and a summary of the eligible articles can be found in Table 3.

Quality assessment

The quality assessment of the retrieved studies was performed using the PEDro scale for bias. This scale has 10 questions and according to Maher et al (2003) it is a reliable and accurate grading system.

DISCUSSION

The aim of this paper is to present the relevant literature and current evidence for the potential use of HFCWO device with COPD patients. In terms of study quality, the four studies included have different sample sizes, outcome measures and comparison groups and their subjects had different stage/acuteness of COPD. As a consequence, a metaanalysis was not appropriate due to the heterogeneity of these studies.

Farag and EL-Syed (2018) found that both HFCWO and flutter groups have a positive effect on the spirometric indices, oxygenation parameters and COPD Assessment Test (CAT) scores in acute exacerbation COPD patients compared to the control group. Both techniques had a good tolerance but no statistically important differences were found between them. It was suggested that this improvement could be potentially from the effect the techniques have on airway clearance. HFCWO produce improvements in gas mixing and homogenisation of alveolar ventilation for previously closed or under ventilated lung units. Flutter enhances movement of secretions from the peripheral to the central airways, improving lung function and oxygenation. As a consequence, it increases oxygen delivery to the tissues which further enhances metabolic activity and thus improving the symptoms. More adverse effects were detected in the flutter group. This was attributed to the flutter being a semi-invasive technique requiring forced expiration which rises the intrathoracic pressure, potentially causing internal damage.

Nicolini et al (2018) suggested that the greater improvement in the IPV group (compared to the HFCWO) in their outcome measures could be due to IPV resolving the obstruction on the small bronchial airways, improving the alveolar ventilation and reducing lung hyperinflation. This further reduced the respiratory workload and improved the patients' symptoms. Also, the changes in the sputum cellularity for both groups (but greater in IPV group), could be due to both techniques having a modulation effect on the inflammatory cells and thus reducing the C-Reactive Protein value (CRP). High CRP indicates an infection which might lead to another exacerbation of COPD and potentially another hospitalisation. The major limitations of this study were its short duration and the absence of sham treatment group to reduce bias on the subjective elements of the outcome measures.

Chakravorty, Chahal and Austin (2011) used a cross-over study design in order for the subjects to act as their own controls. Inclusion and exclusion Criteria of this review.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>People diagnosed with Chronic Obstructive Pulmonary Disease with any degree of severity and state of condition</td>
<td>People diagnosed with pathologies other than Chronic Obstructive Pulmonary Disease</td>
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<td>Adults</td>
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<td>Use of High Frequency Chest Wall Oscillation device</td>
<td>Studies written in other languages</td>
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<tr>
<td>Utility of vest high frequency chest wall oscillation device versus flutter device in acute exacerbation of chronic obstructive pulmonary disease</td>
<td>Farag TS and EL-Syed M (2018)</td>
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<tr>
<td>Safety and effectiveness of the high-frequency chest wall oscillation vs intrapulmonary percussive ventilation in patients with severe COPD</td>
<td>Nicoloni A et al (2018)</td>
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A pilot study of the impact of high-frequency chest wall oscillation in chronic obstructive pulmonary disease patients with mucus hypersecretion

Chakravorty I, Chahal K and Austin, G (2011)

HRQoL (St George's Respiratory questionnaire and self-reported questionnaire) Patient tolerability and compliance Spirometry Wet sputum volume

HFCWO group

Conventional treatment group

4 weeks with 2 weeks wash-out period followed by 4 weeks. HFCWO session lasted for 20 minutes twice per day

Conventional group followed their own COPD management regime (prescribed medication, advice on regular exercise and cough clearance of sputum)

Medications included: long-acting bronchodilator, inhaled corticosteroid, acting anticholinergic inhaler

The SGRQ impact score and the spirometry values - FEV1 (HFCWO group: pre-1.05 L, post-1.07 L, conventional group: pre-0.97 L, post-1.01 L) remained nonsignificant for both groups. Sputum expectoration remained individually variable but showed a trend towards a reduction in HFCWO group. There was a significant improvement in the mean total score in the five-symptom self-reported questionnaire in patients in HFCWO group (p=0.03) SGRQ scores showed significant improvement in the symptom dimension (p=0.028) only in the HFCWO group. No statistically significant improvement in any dimension of the SGRQ scores in the conventional group.

The HFCWO device was well tolerated with good reported compliance

8 participants drop out as they developed exacerbations of COPD

Does high-frequency chest wall oscillation therapy have any impact on the infective exacerbations of chronic obstructive pulmonary disease? A randomized controlled single-blind study

Goktalay T et al (2013)

Saint George's Respiratory Diseases Questionnaire BODE index (Body mass index, FEV1, modifies Medical research council dyspnoea scale and 6 minutes walking test) Exercise capacity Hospitalisation duration Arterial Blood gases analysis

Group 1: control Group 2: HFCWOT

5 days study duration Both groups had general therapy for the infective exacerbation of COPD (controlled oxygen therapy, short-acting b bronchodilator and anti-cholinergic inhaler, 1 mg/kg/day parenteral steroid and antibiotic therapy in case of signs of bacterial infection, pathology-oriented therapy in case of any underlying causes of COPD exacerbations HFCWO group had the standardised medical exacerbation therapy (above) plus HFCWO for 20 minutes, 3 times a day.

3rd day assessment: Both group showed significant improvement in BODE index, FEV1, 6 minutes walking test, PO2 and SpO2 were significantly improved. 5th day assessment: No significant changes were observed in the modified research council scale and PCO2 in group 1 however they were significantly improved in group 2. (Two-group comparisons showed that the difference was not significant) There were no statistically significant differences (p>0.05) in FEV1, MMRC dyspnoea scale, 6 m walking test, BODE index and arterial blood gas parameters between group 1 and 2 at the 3rd and 5th day. However, the most significant changes were observed in FEV1 (group 1: 3%, group 2: 5%) and 6m walking test (group 1: 75m, group 2: 119m) from baseline to day 5.

No significant differences (p=0.527) were observed in the durations of hospitalization between the two group (median duration in both groups to be 7 days)

None reported
own control and thus reduce the inter-subject variability. The authors suggest that it is possible that some of the improvement in the HFCWO group could be attributed to the placebo effect as both groups had positive results. The mucus production was variable in the study, as was the range of Force Expiratory Volume in one second (FEV1). In the participants, however, the results show a positive reduction trend in mucus production in the HFCWO phase compared to the conventional phase. According to the authors, this could be explained by a decrease in the sputum production and the subjects having an efficient mucus clearance. Another explanation could be due to subjects swallowing the phlegm.

Goktalay et al6 (2013) found an improvement in the Partial Pressure of Carbon Dioxide (P,CO₂) and the Medical Research Council (MRC) scale for dyspnoea in the HFCWO group. This could be due to its effect on removing excess mucus and mucus plugs from the peripheral airways, thus improving the gas exchange and the feeling of dyspnoea. These small changes could be attributed to the small sample size, the relatively short duration (5 days) and the single blinded methodology, increasing bias in their results.

Quality of studies

The quality of the studies was average to moderate. Only Farag and Syed’s7 (2018) study failed to randomly allocate their subjects, increasing bias as it reduced the comparability of the groups in terms of intervention and reduced the similarities at baseline between the two groups. Furthermore, only Nicolini et al’s19 (2018) study concealed allocation of the subjects, minimising the allocation bias of the researcher allocating subjects in order to favour a particular group. Also, Goktalay et al’s13 (2013) was the only study that blinded the assessors.

Blinding subjects and therapists is difficult as the techniques used in the studies require special equipment. However, having independent assessors would prevent the researchers from influencing the findings by altering the subjects’ evaluations or encouraging the subjects in one group to do better. Lastly, all studies showed point estimates and variability.

Future Studies

Furthermore, they need to assess the implementation of HFCWO at home, in intensive care unit, its use by the cancer and at earlier stages of COPD. Future studies comparing HFCWO to control or other techniques need to have a larger sample size, longer implementation period, use a sham group and include inflammatory markers as outcome measures. Furthermore, they need to assess the implementation of HFCWO at home, its use by the carer and at earlier stages of COPD.

CONCLUSION:

To conclude, more randomised-controlled trials need to be done comparing HFCWO technique with a larger sample size and a longer trial duration. Overall, HFCWO has positive effects on subjective and objective outcome measures for patients with COPD of varying severity and acuteness. The positive results from the studies included agree with the results from the other studies mentioned above. Only one study mentions adverse effects (mostly haemoptysis). Therefore, physicians might want to consider HFCWO as another tool they can use in patients with COPD, in conjunction with pharmacological treatment. This could potentially facilitate early discharge, better self-management of symptoms, improve the quality of life and lastly reduce the healthcare costs.

FUNDING

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DECLARATION OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
ΠΕΡΙΛΗΨΗ

Αξιολόγηση της εφαρμογής ταλαντώσεων υψηλής συχνότητας στο θωρακικό κλωβό σε ασθενείς με Χρόνια Αποφρακτική Πνευμονοπάθεια

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Ιστορικό
Η συχνότητα εμφάνισης της χρόνιας αποφρακτικής πνευμονοπάθειας αυξάνεται κάθε χρόνο, αυξάνοντας την οικονομική επιβάρυνση του συστήματος υγείας. Η συσκευή ταλαντώσεων τοιχώματος υψηλής συχνότητας (HFCWO) είναι μια τεχνική εκκαθάρισης των αεραγωγών που σύμφωνα με αρκετές μελέτες έχει θετικό όφελος στα συμπτώματα του αναπνευστικού συστήματος που εμφανίζονται στους ασθενείς με κυστική ίνωση και βρογχεκτασίες. Μέθοδος Έγινε αναζήτηση σε επτά βάσεις δεδομένων με αρκετές λέξεις-κλειδί: Αποτελέσματα Τέσσερις μελέτες πληρούσαν τα κριτήρια ένταξης. Συνολικά, οι μελέτες έδειξαν θετικά αποτελέσματα για τη χρήση του HFCWO σε ασθενείς με ΧΑΠ με διαφορετικό στάδιο και οξύτητα. Μόνο μία μελέτα ανέφερε ανεπιθύμητες ενέργειες για τη συσκευή HFCWO. Συμπεράσματα Προσφέρεται η μπορεί να προστεθεί στη θεραπεία του ΧΑΠ, από τους γιατρούς. Ενδείκνυται να γίνουν μελλοντικές μελέτες, με τη χρήση του HFCWO με ασθενείς με ΧΑΠ μεγαλύτερης διάρκειας.


Λέξεις-κλειδία: ΧΑΠ, HFCWO

REFERENCES

Haemorrhagic pulmonary metastases due to choriocarcinoma syndrome

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¹Pulmonary Department, ²Radiology Department, ³Oncology Department, 424 General Military Hospital (424 GMHT), Thessaloniki, Greece

A 55-year-old male patient under chemotherapy for metastatic testicular choriocarcinoma presented in the emergency department of our hospital due to dyspnea and haemoptysis. Chest CT scan revealed a halo of ground glass opacity around most of the preexisting multiple secondary masses and nodules, indicative of peritumoral haemorrhage (CT halo sign) (Fig. 1-3).

Choriocarcinoma is well known to cause haemorrhagic pulmonary metastases, along with angiosarcoma, renal cell carcinoma and melanoma. Testicular choriocarcinoma is a rare aggressive type of non-seminomatous germ cell tumor.

‘Choriocarcinoma syndrome’ is a special feature of choriocarcinoma, first described by Logothetis in 1984, characterised by markedly elevated serum beta-subunit human chorionic gonadotropin (β-hCG) and bleeding in metastatic sites, due to high volume of choriocarcinomatous elements¹. Similarly to our patient’s case, acute pulmonary haemorrhage is choriocarcinoma syndrome’s most common manifestation, but bleeding can occur in any metastatic site, always representing a medical emergency, linked to high mortality and requiring prompt and intensive supportive care².

No funding or conflict of interest is declared.
All authors are in agreement with the manuscript.

REFERENCES
A 47 year old ex-smoker female was admitted to our hospital due to severe hemoptysis and worsening dyspnea and cough, started three days prior to admission. The patient had a history of multiple lung abscesses and empyema of the right lung that required surgical intervention in 1986 and a right lower lobectomy in 1988 due to bronchiectasis and recurrent lung infections. At her last follow up in Israel in 2014, a cystic lesion with a gas-fluid level was detected, but she didn’t receive any treatment for that. During the previous years the patient did not refer to a chest physician for follow up or for any new symptoms.

On admission, the patient was hemodynamically unstable and had respiratory insufficiency. Despite the initial management of the patient, the hemoptysis was only partly faded and there was radiologic worsening. CT scan was performed showing a thick-walled cyst at the right upper lobe with another lesion to be detected inside the cyst. The sputum culture grew Aspergillus Niger, while the rest microbiologic and serological tests were negative. Pulmonary Aspergilloma was considered the most likely diagnosis and antifungal medication (Voriconazole) was added to her therapeutic regimen with a progressively improvement of her clinical status and the complete remission of the hemoptysis. Fifteen days later, quite stable, she was transferred back to her country (Israel) at a thoracic surgery department, where a non-invasive management was decided. Six months later, the patient was clinically and radiologically improved and no recurrence has been observed to date.

The diagnosis of pulmonary aspergilloma should be included in the differential diagnosis also for immunocompetent patients with structural abnormalities of the lung parenchyma.

REFERENCES:

The Scab Sign

Unnati Desai, MD, Jyotsna M. Joshi, MD

Department of Pulmonary Medicine, T.N. Medical College, B.Y.L. Nair Hospital, Mumbai, India

A sixty year-old lady presented with an episode of massive hemoptysis. She had intermittent cough, streaky hemoptysis since two years and pulmonary tuberculosis nine years ago. General and systemic examination was normal except bronchial breathing in the right upper lobe with bilateral crackles. Her blood investigations unveiled diabetes mellitus. Chest X-Ray confirmed a right upper lobe fibrotic collapse. The high resolution computed tomography of thorax reported fibrocystic destruction of right upper lobe, an aspergilloma and a “Scab sign” seen along the superior aspect with fibrocystic destruction of right and left lower lobe (Fig. 1). The bronchoscopy and microbiology testing yielded negative results for fungus and tuberculosis. The patient was diagnosed as a case of chronic pulmonary aspergillosis (CPA)-simple aspergillomas and managed conservatively. The scab sign is characterised by a focal irregular/spiky cavity wall thickening, correlating pathologically with a fibrinopurulent mass and/or blood crust and clinically indicating the site and predisposition to hemoptysis in CPA.1 CPA cases consists of simple aspergillomas vs chronic cavitary/necrotizing pulmonary aspergillosis (CCPA/CNPA). Both may demonstrate hemoptysis as a presenting symptom. While simple aspergillomas have an indolent course and are managed conservatively, CCPA/CNPA also previously known as semi-invasive aspergillosis have symptomatic progressive disease and require treatment with anti-fungal therapy/surgery.2

REFERENCES

2. Patterson KC, Strek ME. Diagnosis and treatment of pulmonary aspergillosis syndromes. CHEST 2014; 146:1358-68.

FIGURE 1.
Διάχυτες Πνευμονοπάθειες
7ο ΕΤΗΣΙΟ ΣΕΜΙΝΑΡΙΟ «ΠΑΛΑΙΑΣ ΒΟΥΛΗΣ»
Η Πνευμονολογία κοντά στον Πνευμονολόγο
16·3·2019
18.00 - 21.00
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ΚΑΒΑΛΑ
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A *running (short) title.*
The total number of words of the manuscript and the abstract.

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A structured abstract should be provided of up to 250 words. It should consist of our paragraphs, labeled Background, Methods, Results, and Conclusions. They should briefly describe, respectively, the problem being addressed in the study, how the study was performed, the most important results, and what the authors conclude from the results. Abbreviations should be avoided and, if used, they should be explained the first time mentioned.

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|-----------------------------------------------|-----------------|-----------------|
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The rationale for the study should be summarized and relevant background material outlined. The Introduction should not contain findings, methods used or conclusions.

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Results should be presented in a rational order in the text, tables and figures. The authors should avoid repetitive presentation of the same data in different forms, especially between the text and tables and figures. The Results should not include material appropriate to the Discussion.

Discussion
The discussion should start by presenting the new and most interesting data of the work in relation to any hypotheses made in the Introduction. Any unexpected or contradictory results should be explained or defended. For example, evaluation of methodology and the associations of new information to the existing knowledge in the topic should be discussed. Speculation should be kept to a minimum. The results must not be simply reiterated. New results should not appear in the Discussion. No specific reference to figures and tables should be included in the Discussion.

Acknowledgements
Acknowledge the persons who provided a true contribution and who endorse the data and conclusions. Acknowledge any funding sources.

References
Only published works may be cited as references. Manuscripts accepted but not yet published may be cited designating the accepting journal, followed by the term (in press), and copies of the in-press articles should be provided for reviewer inspection. References should be cited in the manuscript with superscript numerals in the order in which they appear in the text. The full list of references should be provided in numerical order on a separate page at the end of the text. References should include, in order, the following: authors, title, source, year of publication, volume, and inclusive page numbers. All authors should be listed if they are six or fewer; when they are seven or more, list the first three followed by ‘et al.’ Please abbreviate journal names as in Index Medicus (available at http://www.nlm.nih.gov/tsd/serials/jli.html; accessed on November 9, 2008).

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Double-space tables (including any footnotes) should be presented on separate pages, providing a title for each. Any abbreviations used in a Table should be defined in the Table’s footnote.

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Figures may be inserted in the text file or in a separate file (accepted formats are JPEG, TIFF and EPS). Legends for all figures should be included in the file with the text, on a separate page after the Tables, and should not appear on the actual figures. If photographs of patients are used, they should either not be identifiable or the photographs should be accompanied by written permission to use them.

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