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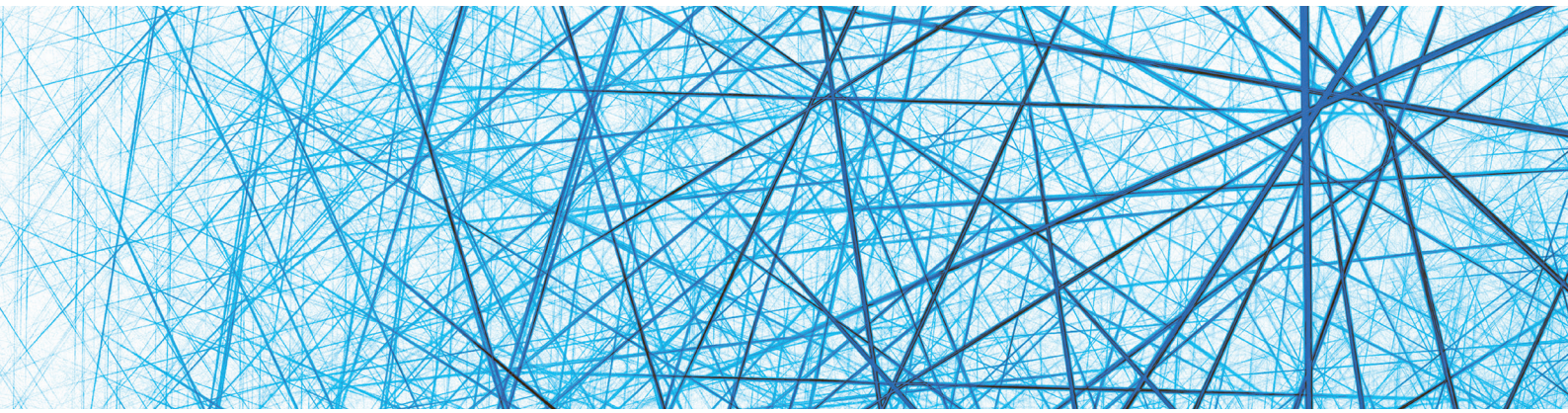

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Barcelona-Boston Lung Conference 2017

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Sumario

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PROLOGUE

On January 20th and 21st, a new edition (the fourth one!) of the 2017 Barcelona-Boston Lung Conference was celebrated. As in the past, this scientific meeting took place at the Paraninfo Hall located at the Faculty of Medicine, University of Barcelona, and was attended by more than 200 pulmonologist, mainly Spanish but with some international presence from Portugal and Latin America. The program included the presentation of the Master Lectures and the discussion (both in front of the poster and after the spoken performance) of the 20 best communications amongst the 150 submitted this year.

The Master Lectures addressed the following topics: pulmonary ageing, multi-resistant tuberculosis, new therapeutic aspects in pulmonary fibrosis, adult respiratory distress syndrome, respiratory muscle failure, relationship of sleep disturbance to cardiovascular pathology and new interventional endoscopic techniques.

The current issue of Archivos de Bronconeumología includes the summary of these Master Barcelona-Boston Lung Conferences, as well as the abstracts of the twenty best communications presented by young researches. As Scientific Directors, we believe that the 2017 Barcelona-Boston meeting was a success due to the high scientific level of the lectures and presentations by young researchers. We are also very satisfied with the participation of the audience while discussing the presentations. We admit, however, that we could be biased. Therefore if you believe that there is any aspect that needs to be improved (as surely there is), please feel free to let us know and we will consider their eventual implementation at the 2018 edition.

We invite you to attend next year to see firsthand the scientific level of the meeting and also to participate as part of the audience, so you can contribute to the ongoing training of us all.

Sincerely,

Àlvar Agustí
Bartolomé Celli
Monograph coordinators

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de Archivos de
Bronconeumología

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EditorialRespira

Monografías de Archivos de Bronconeumología

Invasive bronchology: New frontiers for the pulmonologist

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During the past decade, there has been a remarkable advancement in diagnostic and therapeutic technological innovations in the field of Interventional Pulmonology (IP). This has led to an increased awareness among IP specialists for the importance to validate the clinical and applications of such new technologies toward improving patient care in diseases such as lung cancer and chronic obstructive pulmonary disease (COPD). In this brief article, we will highlight the role of IP in the diagnosis and treatment of solitary pulmonary nodule (SPN) and COPD.

SPNs could be seen in 0.09% to 7% of all chest radiographs.[1] The prevalence of SPNs using CT imaging in large studies on lung cancer screening ranged from 8% to 51%, with prevalence of malignancy from 1.1% to 12%.[1] The National Lung Cancer Screening Trial (NLST) initiated a paradigm shift change in the approach to early detection and mortality reduction from lung cancer in the US with a 20% reduction in lung cancer mortality in the low dose CT (LDCT) screening arm as compared to CXR.[2] Moreover, LDCT was positive in around 24% of screens necessitating further diagnostic interventions using tools with high success rate and safety profile.[3] For SPNs of less than 2 cm, sensitivity of conventional bronchoscopy was only 34% and it was probably influenced by distance from the hilum, air bronchus sign and the lobe or subsegment where the lesion of interest was located.[4] CT-guided transthoracic needle aspiration (CT-TTNA) has a high diagnostic yield for SPNs (up to 95%). However, this was associated with frequent occurrence of pneumothorax (20-25%) with approximately 7% of patients requiring chest tube drainage. Furthermore, certain SPNs remained difficult to access via TTNA approach such as patients with bullous lung disease or lesions that were distant from pleura (diagnostic accuracy dropped to 60% or less when the needle path length exceeded 40 mm).[4,5] Several guided-bronchoscopy technologies such as: electromagnetic navigation bronchoscopy , virtual bronchoscopy , ultrathin bronchoscope and radial probe endobronchial ultrasound with guided sheath have been developed to improve the diagnostic yield of transbronchial biopsy for SPNs diagnosis. A recent meta-analysis showed that the pooled diagnostic yield of guided bronchoscopy using one or a combination of the above modalities was 70% with a pneumothorax rate of 1.5%.[6] However, the yield was 61% for those lesions < 2 cm vs 82% for those > 2 cm and 79% with a bronchus sign vs 31% without a bronchus sign.[6] Recently, a novel bronchoscopic trans-parenchymal nodule access (BTPNA) has been developed that allowed to access nodules through a transparenchymal approach independent of the need to have an airway leading into the lesion. The Archimedes Virtual Bronchoscopy Navigation System (Broncus Medical, Mountain View, Calif., USA) reconstructed CT data into a 3D model which provided guidance of a sheath from the point of entry on the airway wall through the lung parenchyma directly to the SPN using a balloon catheter equipped guided sheath . During the actual procedure, a hole is created in the airway wall at the point of entry with a needle followed by dilating the hole with a balloon, advancing the sheath with blunt stylet through parenchymal tissue in a straight line path to the nodule under real-time fluoroscopy data with the 3D CT data then accessing and sampling the SPN. Two recent pilot studies in humans (total of 18 patients) suggested that BTPNA was feasible in creating an airway exit point and tunneling to the target lesion through the parenchyma with adequate biopsy obtained in 83%.[7,8] Two patients developed pneumothorax in one study with one requiring chest tube drainage while there were no adverse events in the other study.[7,8] Another novel diagnostic tool: electromagnetic navigation system (Veran Medical Technologies Inc, St Louis, MO USA) has been developed to allow bronchoscopists to perform electromagnetic guided transthoracic needle aspiration (ETTNA). It was an accessory device that used electromagnetic navigation to identify an instrument and track its position relative to a CT-based image of the patient's anatomy. A recent pilot study of 24 patients showed that ETTNA was feasible in 96% of cases with a diagnostic yield of 83% alone which increased to 87% with navigational

bronchoscopy and to 92% when combined with EBUS and navigational bronchoscopy. The pneumothorax rate was 21% with 8% requiring chest tube drainage.[9] Furthermore, there have been significant advances in technology investigating the therapeutic role of bronchoscopy for SPNs that are confirmed or highly likely to be malignant. Through guided bronchoscopic techniques, the bronchoscopist could accurately reach peripheral lesions and provide targeted local therapy such as local radiation, heat and cold therapies, and gene-based technologies.[10] Probably in the near future, interventional pulmonologists might be capable of potentially curing malignant disease without surgery when targeted therapy is combined with the tools used in diagnostic bronchoscopy to localize the peripheral tumor.

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by high prevalence with high morbidity and mortality worldwide.[11,12]. The main symptoms of COPD are productive cough, shortness of breath and limited exercise capacity that affects quality of life. These symptoms are caused by increased mucus secretion, bronchial constriction and emphysematous destruction of lung parenchyma associated with dynamic hyperinflation.[13] Thus, COPD is regarded as a syndrome with various phenotypes that depends on which clinical symptoms and pathophysiological aspects are predominant (i.e. emphysema or chronic bronchitis). Currently, the main goal of therapy is symptomatic relief, improvement of quality of life and prevention of COPD progression. Non-pharmacologic therapeutic strategies includes smoking cessation, pulmonary rehabilitation and vaccinations (influenza and pneumococcal).[14] Pharmacotherapy of COPD consists of inhaled anticholinergics, β2 agonists, inhaled corticosteroids and phosphodiesterase inhibitors and long-term oxygen therapy. However, in a selected subgroup of patients with predominant emphysema and hyperinflation, lung volume reduction surgery (LVRS) represents a further treatment option. Minimizing hyperinflation allows the diaphragm to function more effectively, increases lung elastic recoil leading to improved respiratory mechanics. The National Emphysema Treatment Trial (NETT), published in 2003, showed that LVRS achieved significant improvements in mortality, exercise capacity and quality of life in patients with predominantly upper-lobe emphysema and low exercise capacity.[15] However, postoperative mortality (8%) and morbidity (60%) was high after 90 days especially in patients with low FEV_1 and homogenous emphysema distribution or low DLCO. These findings stimulated the development of minimally invasive lung volume reduction procedures with the goal of reducing peri-interventional morbidity and mortality.

Endoscopic lung volume reduction (ELVR) was introduced in 2003 and developed rapidly during the past decade. Currently, different endoscopic therapeutic techniques are presently available for COPD: valve implantation, lung volume reduction coil (LVRC) implantation and targeted lung denervation (TLD). So far, valves have remained the best studied ELVR technique. These one-way valves completely occluded the target lobe allowing the air to exit during expiration without entering during inspiration, thus facilitating lobar atelectasis. Two different types of valves are currently available that differ in shape but with similar mechanism of action: the endobronchial valves (EBV; Zephyr, Pulmonx Inc., Redwood City, CA) and intrabronchial valves (IBV; Spiration, Olympus, Tokyo, Japan).

Several randomized controlled trials have been published regarding valves therapy as a unilateral treatment for a targeted lobe.[16-21] When taking all these trials together, evidence is accumulating that such treatment is effective (even as high as a 75% in improving lung function, quality of life as well as exercise capacity) in a properly selected population with emphysema (homogenous or heterogeneous) having: (1) complete or near complete fissure (> 85%) intact interlobar fissure between the treatment target lobe and adjacent lobe and/or (2) absence of collateral flow assessed with a high resolution chest CT scan and a Chartis system.[16-21] The major adverse events following valve placement are COPD exacerbations and pneumothorax (estimated as 20%).

LVRC (PneumRx/BTG, Camberley, UK) was another bronchoscopic bilateral sequential implantation technique of several nitinol coils aiming to achieve parenchymal compression due to the preformed coiled shape, improve elastic recoil and reduce trapped airspace independent of collateral ventilation. In a recent randomized controlled multi-center trial, LVRC resulted in a modest non-clinically improvement in exercise capacity as compared to usual care in patients with emphysema and hyperinflation. However, post hoc analysis revealed that patients with heterogeneous emphysema and severe hyperinflation (RV> 225%) experienced a clinically significant improvement in lung function, exercise capacity and quality of life.[22]

TLD (Holaira, Minneapolis, MN) provided an ablative therapy through radiofrequency energy into the main bronchus that targeted the parasympathomimetic innervation of the airways and simulated the effect of anticholinergic drugs in patients with COPD that demonstrates positive bronchodilator response to inhaled anticholinergic medication. One recent pilot study[23] showed that bronchoscopic TLD was feasible, safe and well tolerated and further trials are needed to support such preliminary results as well as demonstrate efficacy. Currently, randomized clinical trials are being done in Europe.

In conclusion, current endoscopic diagnostic and therapeutic techniques are significantly progressing for SPNs and COPD. The new technologies look promising but await further clinical studies to confirm their efficacy.

References

1. Patel VK, Naik SK, Naidich DP, Travis WD, Weingarten JA, Lazzaro R, et al. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 1: radiologic characteristics and imaging modalities. Chest. 2013 Mar;143(3):825–39.

2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.

3. Aberle DR, Abtin F, Brown K. Computed tomography screening for lung cancer: has it finally arrived? Implications of the national lung screening trial. J Clin Oncol 2013;31:1002–8.

4. Hergott CA, Tremblay A. Role of bronchoscopy in the evaluation of solitary pulmonary nodules. Clin Chest Med. 2010;31(1):49–63.

5. Cham MD, Lane ME, Henschke CI, Yankelevitz DF. Lung biopsy: special techniques. Semin Respir Crit Care Med. 2008;29(4):335–49.

6. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest. 2012 Aug;142(2):385–93.

7. Herth FJ, Eberhardt R, Sterman D, Silvestri GA, Hoffmann H, Shah PL. Bronchoscopic transparenchymal nodule access (BTPNA): first in human trial of a novel procedure for sampling solitary pulmonary nodules. Thorax 2015;70:326–32.

8. Harzheim D, Sterman D, Shah PL, Eberhardt R, Herth FJ. Bronchoscopic Transparenchymal Nodule Access: Feasibility and Safety in an Endoscopic Unit. Respiration. 2016;91(4):302–6.

9. Yarmus LB, Arias S, Feller-Kopman D, Semaan R, Wang KP, Frimpong B, et al. Electromagnetic navigation transthoracic needle aspiration for the diagnosis of pulmonary nodules: a safety and feasibility pilot study. J Thorac Dis. 2016 Jan;8(1):186–94.

10. Harris K, Puchalski J, Sterman D. Recent Advances in Bronchoscopic Treatment of Peripheral Lung Cancers. Chest. 2016 Jun 9.

11. Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013;369(5):448–57.

12. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–65.

13. Celli BR, Cote CG, Marin MJ, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005–12.

14. Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2015.

15. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059–73.

16. Sciurba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233–44.

17. Herth FJ, Noppen M, Valipour A, Leroy S, Vergnon JM, Ficker JH, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J 2012;39:1334–42.

18. Ninane V, Geltner C, Bezzi M, Foccoli P, Gottlieb J, Welte T, et al. Multicentre European study for the treatment of advanced emphysema with bronchial valves. Eur Respir J 2012;39: 1319–25.

19. Davey C, Zoumot Z, Jordan S, McNulty WH, Carr DH, Hind MD, et al. Bronchoscopic lung volume reduction with endobronchial valves for patientswith heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. Lancet 2015;386:1066–73.

20. Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. N Engl J Med. 2015 Dec 10;373(24):2325–35.

21. Valipour A, Slebos DJ, Herth F, Darwiche K, Wagner M, Ficker JH, et al. Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. Am J Respir Crit Care Med. 2016 Nov 1;194(9):1073–82.

22. Sciurba FC, Criner GJ, Strange C, Shah PL, Michaud G, Connolly TA, et al. Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe Emphysema: The RENEW Randomized Clinical Trial. JAMA. 2016 May 24-31;315(20):2178–89.

23. Slebos DJ, Klooster K, Koegelenberg CF, Theron J, Styen D, Valipour A, et al. Targeted lung denervation for moderate to severe COPD: a pilot study. Thorax. 2015 May;70(5):411–9.

EditorialRespira

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ARDS – Maintaining gas exchange while limiting iatrogenic lung injury: A delicate balance

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Mechanical ventilation is a life-saving therapy for many patients with acute respiratory failure. However, over the past ~20 years, it has become increasingly apparent that mechanical ventilation can have serious adverse consequences, including increased risk of nosocomial pneumonia, impaired cardiac function, and ventilator-induced lung injury (VILI)[1,2]. This iatrogenic nature of mechanical ventilation is particularly problematic for patients with the Acute Respiratory Distress Syndrome (ARDS), where mechanical ventilation can be a major factor leading to the death of some patients. This brief review will summarize some key concepts related to our increasing understanding of the iatrogenesis associated with mechanical ventilation, and describe the importance of lung protective ventilation for ARDS patients as well as for non-ARDS patients.

In the 1960's maintenance of normal $PaCO_2$ and PaO_2 were viewed as the critical goal of mechanical ventilation. Anesthesiologists realized that patients in the operating room developed atelectasis and hypoxemia if they were ventilated with small tidal volumes[3]. To solve this problem, they started using ventilation strategies with very high tidal volumes to re–open those regions of the lung that were collapsed at end-expiration. Clinicians and researchers saw this as beneficial because large tidal volume (Vt) ventilation reduced ventilation–perfusion mismatch, meaning there was less need for high oxygen fractions. ICUs at the time were largely run by anesthesiologists, and thus the high Vt strategy was used outside the operating room for patients with acute respiratory failure. The thought was that ARDS patients, hypoxemic to start, would similarly suffer from atelectasis and worsening hypoxemia.

Despite sporadic articles in the 1960s and '70s (e.g. Webb and Tierney) describing the harm of large tidal volumes in animals, this concept was not adopted by clinicians. At the time, getting the blood gases right was the imperative. For example, in 1979 the late Roger Bone published an abstract in which he investigated factors associated with pulmonary barotrauma. 40% of patients had severe barotrauma: the mean Vt used was 22+4 ml/kg based on measured body weight!

In the last two decades animal research increasingly and convincingly demonstrated that high tidal volumes could induce VILI. In the late 1980s Dreyfuss and colleagues determined that lung stretch was a critical factor leading to VILI; they coined the term volutrauma to highlight the fact that it was not the airway pressure per se that was important, but the lung stretch[4]. In the 90's we demonstrated that ventilatory strategies that allowed recruitment and de-recruitment of lung units could lead to significant lung injury including development of hyaline membranes[5]. In 1997, we identified a mechanism of injury that we called biotrauma, i.e., the biological consequences associated with mechanical ventilation[6]. We showed that injurious forms of ventilation, i.e. those that promote atelectrauma and/or over-distension could lead to release of mediators in the lung. Coupled with the increased permeability due to the underlying disease being treated (e.g. ARDS), or the increased permeability caused by overdistension, mechanical ventilation could lead to translocation of mediators, bacteria or endotoxin into the systemic circulation. This in turn could cause end-organ dysfunction distal to the lung (e.g. kidneys) and lead to multi-organ failure[7]. This mechanism could explain the fact that most patients with ARDS who die, do so not because of hypoxemia but because of multi-organ failure.

To mitigate VILI Hickling and colleagues used a very intriguing strategy in treating their ARDS patients. They realized that patients that with ARDS usually die of multiple system organ failure, not hypoxemia; and that respiratory acidosis is very well tolerated if the patient is not hypoxemic. As such, they prioritized a ventilatory strategy in which limiting lung stretch (to limit VILI) was more important than the maintenance of normal blood gases. Their strategy, which they called permissive hypercapnia, demonstrated a decrease in mortality compared to a historical control group. The mean value of PCO_2 was 66 mmHg, with one patient reaching a PCO_2 of 158 mmHg; the lowest pH was 6.79[8]. This strategy was similar to a strategy called controlled hypoventilation which was used successfully to treat patients with status asthmaticus; essentially: less ventilation leads to less iatrogenesis.

A number of years later, a landmark article published by the ARDS Network definitely demonstrated the beneficial effects of ventilation with low tidal volumes in patients with ARDS[9]. They compared a strategy using low tidal volumes (6 ml/kg predicted body weight (PBW)) to higher tidal volumes (12 ml/kg PBW). Ventilation with low tidal volumes resulted in a 9% absolute decrease in mortality and increased the number of ventilator–free days. Some clinicians and investigators were relatively slow to accept these findings, but subsequent trials and a meta-analysis convincingly confirmed the reduction in mortality by using low tidal volumes in patients with ARDS. Currently, lung–protective ventilation with low tidal volumes is considered standard of care for patients with ARDS.

This study was followed by other randomized controlled clinical trials (RCTs) addressing various approaches for minimizing VILI including use of higher PEEP levels[10], prone position[11], and early, short-term neuromuscular blockade[12]. Lung protective strategies are currently the standard of care for patients with ARDS.

There is also increasing evidence that these strategies are also important in ventilating patients who do not have ARDS. Recent evidence has demonstrated that the use of lung protective strategies can improve post-operative outcomes in patients undergoing major abdominal procedures[13], can prevent patients with normal lungs being ventilated in the ICU from developing ARDS[14], and can lead to an increase in the number of usable lungs from brain dead patients for subsequent lung transplantation[15].There are also ongoing studies examining whether VILI can be completely abrogated by the use of extra-corporeal lung support to decrease the intensity of mechanical ventilation or to even completely abolish it by using full support with ECMO.

In summary, this change in philosophy from focusing solely on the maintenance of normal blood gases to a focus on mitigating lung injury while maintaining "adequate" gas exchange has dramatically changed the way patients are being ventilated world-wide. It is also in synch with other evidence that "more may be less" (e.g. transfusions, anti-arrhythmia therapies) as we care for our sickest patient.

References

1. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2013; 369(22):2126–36.
2. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis 1974;110(5):556–65.
3. Bendixen HH, Hedley-Whyte J, Laver MB. Impaired Oxygenation in Surgical Patients during General Anesthesia with Controlled Ventilation. A Concept of Atelectasis. N Engl J Med 1963;269:991–6.
4. de Prost N, Ricard JD, Saumon G, Dreyfuss D. Ventilator-induced lung injury: historical perspectives and clinical implications. Ann Intensive Care 2011;1(1):28.
5. Muscedere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 1994;149(5):1327–34.
6. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 1997;99(5):944–52.
7. Slutsky AS, Tremblay LN. Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 1998;157(6 Pt 1):1721–5.
8. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 1994;22(10):1568–78.
9. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342(18):1301–8.
10. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010;303(9):865–73.
11. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159–68.
12. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363(12):1107–16.
13. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013;369(5):428–37.
14. Serpa Neto A, Nagtzaam L, Schultz MJ. Ventilation with lower tidal volumes for critically ill patients without the acute respiratory distress syndrome: a systematic translational review and meta-analysis. Curr Opin Crit Care 2014;20(1):25–32.
15. Mascia L, Pasero D, Slutsky AS, Arquis MJ, Berardino M, Grasso S, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. JAMA 2010;304(23):2620–7.

EditorialRespira

Monografías de Archivos de Bronconeumología

Accelerated ageing in COPD: New insights and targets

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COPD is characterised by acceleration of the ageing process in lung parenchyma and airways and is commonly associated with comorbidities, such as cardiovascular and metabolic diseases, which also may share these mechanisms. There is now a much better understanding the signalling pathways and cellular events involved in ageing, including evidence of cellular senescence with telomere shortening, activation of phosphoinositide-3-kinase(PI3K)-mammalian target of rapamycin (mTOR) signalling, impaired autophagy, mitochondrial dysfunction, stem cell exhaustion, epigenetic changes and abnormal microRNA profiles[1]. All of the hallmarks of ageing have now been identified in COPD patients and there is an accumulation of senescent cells in the lungs[2,3]. It used to be thought that senescent cells were basically inert but it is now evident that they secrete a particular combination of inflammatory proteins, known as the senescence-associated secretory phenotype (SASP), including TNF-α, IL-1β, IL-6, CCL2, CXCL1, CXCL8, TGF-β, MMP-9, all of which are increased in COPD[4]. Removal of senescent cells ($p16^{INK4a+}$) in old mice prolongs their lifespan and reduces the incidence of age-related diseases, such as cardiovascular disease and chronic kidney disease[5]. COPD patients also show evidence for increased immunosenescence, with senescent CD4+ and CD8+ T lymphocytes ($CD28^{null}$), which are less able to mount an immune response and associated with autoimmunity[6]. Many of these ageing pathways are driven by chronic oxidative stress, a key driving mechanism of COPD pathology[7]. There is also a reduction in endogenous anti-ageing molecules, which further accelerates the ageing process. Many endogenous anti-ageing molecules have been identified and all appear to be reduced in COPD, including histone-deacetylase-2, Nrf2, Klotho, SMP30[8]. In COPD patients there is a selective reduction in sirtuin-1 and sirtuin-6, which may result in the characteristic changes in the lungs of COPD patients, but also in associated comorbidities[9]. Reduced SIRT1 is linked to defective autophagy, reduced DNA repair, mitochondrial dysfunction, increased activation of inflammatory genes (through increased NF-κB), whereas decreased SIRT6 results in defective Wnt signalling, reduce telomere length and reduced Nrf2 expression.

It is now recognised that micro-RNAs and other non-coding RNAs, play a key role in the dysregulation of signalling pathways in chronic disease. In particular miR-34a has been shown to be an important regulator of SIRT1 and we have shown that is also regulates SIRT6, but not the other 5 sirtuins known. There is a marked increase in miR-34a in COPD lungs and cells, which correlates with reduced SIRT1/6 and increased cellular senescence and is driven by oxidative stress through activation of PI3K/mTOR signalling. By specifically blocking miR-34a with an antagomir, we can restore SIRT1/6 and reduce senescence in COPD small airway epithelial cells[10].

The same pathways are operative in other diseases of accelerated ageing, including cardiovascular diseases, chronic kidney disease and type 2 diabetes; it may be that these common pathways are coordinated through the release of extracellular vesicles, such as exosomes, which may spread senescence[11]. This may account for the comorbidities of COPD and for multimorbidity[12]. Understanding the molecular mechanisms involved in accelerated ageing has identified novel therapeutic targets and several drugs have already been developed that may reduce the ageing process, as well as lifestyle interventions, such as diet and physical activity. This indicates that in the future new treatment approaches may target the common pathways involved in multimorbidity.

References

1. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153(6):1194–217.
2. Mercado N, Ito K, Barnes PJ. Accelerated ageing in chronic obstructive pulmonary disease: new concepts. Thorax 2015;70:482–9.
3. Barnes PJ. Senescence in COPD and its comorbidities. Annu Rev Physiol 2017; Feb 10;79:517-39.
4. Salama R, Sadaie M, Hoare M, Narita M. Cellular senescence and its effector programs. Genes Dev 2014;28:99–114.
5. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 2016;530:184–9.
6. Masters AR, Haynes L, Su DM, Palmer DB. Immune senescence: significance of the stromal microenvironment. Clin Exp Immunol 2017;187:6–15.
7. Kirkham PA, Barnes PJ. Oxidative stress in COPD. Chest 2013;144:266–73.
8. Gao W, Yuan C, Zhang J, Li L, Yu L, Wiegman CH, et al. Klotho expression is reduced in COPD airway epithelial cells: effects on inflammation and oxidant injury. Clin Sci 2015;129:1011–23.
9. Nakamaru Y, Vuppusetty C, Wada H, Milne JC, Ito M, Rossios C, et al. A protein deacetylase SIRT1 is a negative regulator of metalloproteinase-9. FASEB J 2009;23:2810–9.
10. Baker J, Vuppusetty C, Colley T, Papaioannou A, Fenwick P, Donnelly L, et al. Oxidative stress dependent microRNA-34a activation via PI3Kα reduces the expression of sirtuin-1 and sirtuin-6 in epithelial cells. Sci Rep 2016;6:35871.
11. Fujita Y, Kosaka N, Araya J, Kuwano K, Ochiya T. Extracellular vesicles in lung microenvironment and pathogenesis. Trends Mol Med 2015;21:533–42.
12. Barnes PJ. Mechanisms of development of multimorbidity in the elderly. Eur Respir J 2015;45:790–806.

EditorialRespira

Monografías de Archivos de Bronconeumología

Sleep, the dreams and the heart. Emphasis on central sleep apnea

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Normally as sleep deepens from N1 to N3, there is an orchestrated progressive reduction in central nervous system sympathetic outflow associated with an increase in parasympathetic activity. The hemodynamic manifestations of these favorable changes in autonomic activity are a clinically significant reduction in systemic blood pressure and a reduction in heart rate. For these reasons, non-REM sleep which accounts for 80% of total sleep time is peaceful for the cardiovascular system. Not surprisingly, multiple studies have shown decreased acute cardiovascular events during sleep compared to wakefulness, although other factors also contribute to these temporal associations.

Meanwhile sleep could be disrupted by the number of sleep disorders including sleep-related breathing disorders, specifically sleep apneas and hypopneas, both obstructive and central disordered breathing events. The repetitive cycles of apnea and the following compensatory hyperpnea are associated with overnight adverse cardiovascular consequences which include altered blood gas chemistry with recurrent episodes of hypoxia- reoxygenation and ups and downs in arterial PC02, arousals, and augmented swings in negative intrathoracic pressure. These sleep-related breathing disorder consequences are qualitatively similar for both phenotypes of sleep apnea, with acute and chronic hemodynamic, inflammatory and oxidative stress on the cardiovascular system.

Sleep related breathing disorders are quite common in patients with left ventricular systolic and diastolic dysfunction with or without heart failure syndrome. Worldwide, many laboratories have reported on the prevalence of sleep apnea in patients with various cardiovascular disorders. In regard to heart failure, 52% of those with reduced ejection fraction and 48% of those with preserved ejectionfraction suffer from obstructive and central sleep apnea. Frequently these 2 phenotypes are observed in the polysomnogram of the patients.

As noted above, long-term pathobiological derangements of sleep apnea including up-regulation of neurohormonal activity, oxidative stress and inflammation result in endothelial dysfunction. Both obstructive and central sleep apnea could result in a vicious bidirectional cycle between heart failure and sleep apnea with important consequences of hospital readmissions and premature mortality.

That treatment of sleep-related breathing disorders in heart failure is multifaceted and includes optimization of pharmacological therapy with the aim of optimizing cardiovascular function, avoidance of smoking and alcoholic beverages, improved sleep hygiene, exercise and weight loss when applicable. A specific therapy of sleep apnea depends primarily on the phenotype. For obstructive sleep apnea the use of continuous positive airway pressure is the choice among multiple positive airway pressure devices available globally. Although no randomized clinical trial has yet been reported, observational studies consistently show that treatment of OSA with continuous positive airway pressure devices improves left ventricular ejection fraction (in heart failure with reduced ejection fraction), improves diastolic dysfunction (in those with preserved ejection fraction), readmission to the hospital and mortality. This was best observed in a US study of a large cohort of Medicare beneficiaries in which those who were diagnosed with OSA and treated had reduced hospitalization and improved survival. The field however is hungry for randomized clinical trials, involving heart failure patients with both reduced and preserved ejection fraction.

The initial approach to the treatment of central sleep apnea is appropriate evidence-based pharmacological therapy and CRT when applicable. Improvement in cardiopulmonary function has been shown to improve central sleep apnea. Regarding CRT multiple studies have shown that in those individuals in whom CRT improves cardiac function central sleep apnea improves. This is in contrast to lack of improvement in obstructive sleep apnea with CRT in most studies.

SPECIFIC THERAPY OF CENTRAL SLEEP APNEA. PHARMACOLOGICAL THERAPY

The author has performed randomized clinical trials using acetazolamide and theophylline to treat central sleep apnea in heart failure with reduced ejection fraction. Both medications improve central sleep apnea. However long-term studies are not available. Oxygen is also a potent medication for treatment of central sleep apnea and is discussed later.

POSITIVE AIRWAY PRESSURE DEVICES

Continuous positive airway pressure (CPAP) devices have been used to treat central sleep apnea in patients with heart failure and reduced ejection fraction. In the post hoc analysis of the Canadian CPAP trial, survival improved in those patients with heart failure and reduced ejection fraction who responded to CPAP. In these patients the average AHI decreased from about 40/h of sleep at baseline to a mean of 6 per hour of sleep after 3 months of use of CPAP. In contrast, in those patients in whom CPAP failed to attenuate central sleep apnea, mortality increased early on with theuse of CPAP.

The author has reported that in those heart failure patients whose sleep apnea responds to CPAP, there was a considerable reduction in nocturnal arrhythmias which was in contrast to those who did not respond to CPAP.

lt is noted that the number of CPAP-nonresponders is significant varying from 40-50% of patients with heart failure reduced ejection fraction with central sleep apnea.

For these reasons a new device called adaptive servo ventilation was created. This device has gone through generations with improved algorithms. In the most recent generation, the positive end expiratory pressure automatically changes in response to the dynamics of upper airway obstruction. Furthermore, the algorithm of inspiratory pressure support has become much more friendly. The other virtues include an automatic breath nüe, providing a mandatory breath if breathing ceases for a few seconds, aborting any impending apnea. The inspiratory pressure support is variable and anti-cyclic to the pattern of breathing of the patient, with the pressure support increasing when the patient's ventilation decreases, and in contrast, the inspiratory pressure support with decrease when the patient's ventilation increases. With all these virtues, multiple observational, and a few small randomized trials and meta-analyses show the superiority of adaptive servo ventilation when compared to other devices.

lt was with the greatest surprise, when a large randomized trial showed that treatment with adaptive servo ventilation did not improve hospitalization and mortality of patients with heart failure and reduced ejection fraction and central sleep apnea. lt was most surprising that ASV use was associated with excess cardiovascular mortality. Following these results, the manufacturers of ASV devices declared that ASV use should be contraindicated in this population. This single the study changed the practice of sleep medicine for thousands of patients with heart failure and reduced ejection fraction suffering from central sleep apnea.

The author along with several other individuals analyzed the above trial carefully and concluded that there were major pitfalls in the study. Most importantly the device used was the old generation adaptive Servo ventilation which is no longer manufactured by the company who supported the study.

Currently, there is another randomized trial in progress, the advent heart failure using an upgraded adaptive Servo ventilation device with a different algorithm and equipped with automatic end expiratory positive pressure responding to upper airway obstruction.

NON-MASK THERAPY OF CENTRAL SLEEP APNEA IN HEART FAILURE AND REDUCED EJECTION FRACTION

One of the reasons that adaptive servo ventilation might have failed to improve survival could have been due to the increased intrathoracic pressure associated with use of the device, a scenario similar to that observed in the Canadian CPAP trial. The notion here is that the increased intrathoracic pressure imposed by the device could have resulted in adverse hemodynamic effects involving the right ventricle, increasing the afterload while decreasing preload.

Consequently, interest has risen in two other therapeutic options. The first is phrenic nerve stimulation, a transvenously placed lead stimulating a hemidiaphragm resulting in normal breathing during sleep. The results of a randomized trial has been published. The study involved 31 centers in Europe and the USA. 151 eligible patients were randomly assigned to the treatment (n=73) or control groups. The primary effectiveness outcome was a comparison of the proportion of patients in the treatment versus control groups achieving a reduction in AHI of 50% or greater from baseline to 6 months. These patients suffered from severe central sleep apnea. The average AHI decreased from 50/per hour of sleep to 26, a reduction of a magnitude to that of the CANPAP trial, with the difference that these patients suffered from a more sever sleep apnea when compared to those in the CANPAP trial (average AHI=40). Consequent to the reduction in AHI, arousal index and desideration during sleep decreased and importantly patient global assessment improved significantly. Additional analysis is in progress to determine any differences in the rate of hospitalization between the two arms.

The other therapeutic option that has attracted attention is the use of nocturnal oxygen which has been shown to be effective in the treatment of central sleep apnea. Multiple studies, both observational and randomized have shown improvement in central sleep apnea, arousals and most importantly in virtual elimination of hypoxic burden. In two randomized trials, left ventricular ejection fraction increased in association with treatment of central sleep apnea in patients with heart failure and reduced ejection fraction. A large randomized trial powered to detect differences in hospital admission-readmission and mortality is necessary.

References

1. Javaheri S, Barbe F, Campos-Rodríguez F, Dempsey JA, Khayat R, Javaheri S, et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. J Am Coll Cardlol 2017;69:841–58.
2. Javaheri S. Heart failure. In: Principles and Practices of Sleep Medicine, 6/e. Edited by Kryger MH, Roth T, Dement WC; WB Saunders, Philadelphia 2017;1271–85.
3. Javaheri S, Brown LK, Randerath W, Khayat R. SERVE-HF: More questions than answers. Chest 2016;149:900–4.

4. Artz M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, et al., for the CANPAP lnvestigators. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation 2007;115:3173–80.

5. Javaheri S, Germany R, Greer JJ. Novel therapies for the treatment of central sleep apnea. Sleep Medicine Clinics. 2016;11(Issue 2):227–39.

6. Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, et al. Transvenous neurostimulation for central sleep apnoea: a randomized controlled trial. The Lancet 2016;338:973–82.

EditorialRespira

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Re-dimensioning the treatment paradigm in idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF), the prototypic disorder among the group of interstitial lung diseases (ILD), is a chronic progressive fibrotic lung disease characterized by an estimated median survival of approximately three years from diagnosis[1,2]. Although the cause of IPF remains elusive, the main pathogenetic mechanisms have been explored and partly clarified in recent years. In areas of active fibrosis, fibroblasts proliferate and differentiate into myofibroblasts that produce excess extracellular matrix components including collagen and fibronectin under control of pro-fibrogenic stimuli such as transforming growth factor beta[3]. As excess ECM is deposited scar tissue replaces healthy tissue, thereby destroying the complex and delicate alveolar architecture, thus leading to decreased lung compliance, disrupted gas-exchange, and ultimately respiratory failure and death.

After decades of failing clinical trials, finally a few years ago two molecules were shown to be safe and effective in reducing disease progression in IPF[4-6]. This has been an historical and crucial turning point for the management of these patients, particularly after many years of using harmful empiric combinations of corticosteroids and immunosuppressive drugs[7]. Nonetheless, despite the approval of these two anti-fibrotic therapies, nintedanib and pirfenidone, many questions remain unanswered. For example, why are these therapies effective when so many putative anti-fibrotic therapies failed in randomized controlled trials? Which study design will best enable future putative anti-fibrotic therapies to demonstrate efficacy in an era of approved therapies? Will patients with other progressive fibrotic lung diseases respond to treatments which have been shown to be safe and effective for IPF?

The results of many different studies would need to be discussed and analyzed to answer these questions and many of them would remain unanswered anyway. However, one major point is worth discussing. Recent genetic findings have the potential to transform our understanding of IPF, with increasing evidence that inherited genetic factors are significantly associated with the risk of developing pulmonary fibrosis[8]. Genome-wide association studies have identified more than a dozen common genetic variants associated with IPF risk[9-10]. Overall, dramatic advances have been made in our understanding of how the genetic background of an individual might impact on the probability of developing pulmonary fibrosis, the disease course, and potentially response to pharmacologic therapy[11-15]. Findings suggesting the importance of defects in host defense pathways have the potential to inform our understanding of disease pathogenesis. It is now clear that all future clinical trials must control, and perhaps even consider stratifying, for the presence of prognosis-modifying genetic variants. Whether these findings will ultimately translate to clinical practice is however yet to be determined, and robust prospective studies are required to better understand whether genetic factors may influence the diagnosis and treatment of fibrotic ILDs.

Finally, recent reviews have identified the progress that has been made in clinical trial design in IPF, culminating in robust large scale phase III clinical trials demonstrating therapeutic efficacy[16-17]. Following a period of debate, forced vital capacity was accepted as a clinically relevant primary efficacy measure in IPF, and in placebo-controlled trials this enabled demonstration of efficacy of both pirfenidone and nintedanib for regulatory approval[6]. As a new era of clinical trials commences, a particular challenge will be selection of a new primary end-point with sufficient power to enable a feasible study size for late phase clinical trials which are anticipated to be either additive to standard of care (pirfenidone or nintedanib) or head-to-head.

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med 2011;183:788–824.
2. Ley B, Collard HR, King TE. Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2011;183:431–40.
3. King TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. The Lancet 2011;378:1949–61.
4. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. N Engl J Med 2014;370:2071–82.
5. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. N Engl J Med 2014;370:2083–92.
6. Karimi-Shah BA, Chowdhury BA. Forced Vital Capacity in Idiopathic Pulmonary Fibrosis - FDA Review of Pirfenidone and Nintedanib. N Engl J Med 2015;372:1189–91.
7. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. The Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis. N Engl J Med 2012;366:1968–77.
8. Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. Eur Respir J 2015;45:1717-27.
9. Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. Nature Genet 2013;45:613–20.
10. Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huany Y, et al. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. Lancet Respir Med 2013;1:309–17.
11. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med 2011;364:1503–12.
12. Hunninghake GM, Hatabu H, Okajima Y, Gao W, Dupuis J, Latourelle JC, et al. MUC5B Promoter Polymorphism and Interstitial Lung Abnormalities. N Engl J Med 2013;368:2192-200.
13. Zhang Y, Noth I, Garcia JGN, Kaminski N. A variant in the promoter of MUC5B and idiopathic pulmonary fibrosis. N Engl J Med 2011;364:1576–7.
14. Peljto AL, Zhang Y, Fingerlin TE, Ma SF, Garcia JG, Richards TJ, et al. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. JAMA 2013;309:2232–9.
15. Oldham JM, Ma SF, Martinez FJ, Anstrom KJ, Raghu G, Schwartz DA, et al. TOLLIP, MUC5Band the Response to N-acetylcysteine Among Individuals with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2015;192:1475–82.
16. Jones MG, Fletcher S, Richeldi L. Idiopathic Pulmonary Fibrosis: Recent Trials and Current Drug Therapy. Respiration 2013;86:353–63.
17. Collard HR. Where do we go from here? Clinical drug development in idiopathic pulmonary fibrosis. Eur Respir J 2015;45:1218–20.

EditorialRespira

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Drug resistant tuberculosis (DR-TB): A real problem?

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The widespread and sometimes inappropriate use of rifampicin (R) over the past 40 years has given rise to a growing number of rifampicin-resistant tuberculosis (RR-TB) cases, which has become the most decisive factor in the prognosis of TB patients. Treating TB without rifampicin involves long-term therapy over several months with less effective and more toxic drugs[1], resulting in a cure rate of just 50%[2]. In addition, more than 90% of RR-TB patients are also resistant to isoniazid (H)[1], and this condition is known as multidrug-resistant TB (MDR-TB). More and more cases of RR-TB/MDR-TB are being identified each year. Of the 10.4 million cases of TB diagnosed worldwide in 2015, 580,000 were RR-TB/MDR-TB[2]. Of these, more than half had not previously been treated for TB[2], thus showing that there is active community transmission of these forms of TB. Globally, 3.9% of previously untreated TB cases (initial or primary MDR-TB), and 21% of previously treated cases are identified as RR-TB/MDR-TB. The mortality rate has risen to 250,000 cases[2]. The problem further intensifies with the onset and spread of what is known as extensively drug-resistant TB (XDR-TB), which is characterised by MDR-TB plus extensive resistance to fluoroquinolones (FQs, levofloxacin and/or moxifloxacin) and second-line injectables (SLIs, amikacin and/or capreomycin and/or kanamycin). These are the two most active second-line drug groups currently available and the only ones to offer a potential cure to patients with RR-TB/MDR-TB[1]. It is estimated that around 10% of MDR-TB cases are XDR-TB[2].

The situation is further exacerbated by the fact that only 25% of MDR-TB patients have access to effective treatment and only 52% of these are successfully cured (30% of XDR-TB patients). In other words, only around 10% of all MDR-TB cases worldwide are being cured[2]. With these outcomes it is clear that any benefit achieved will only affect individual patients with a practically negligible epidemiological impact, thus giving rise to an uncontrolled epidemic.

In Spain, however, the RR-TB/MDR-TB outlook is fortunately much more favourable, thanks in large part to the historical effective clinical management of TB cases[3].

To attempt to control the worldwide MDR-TB epidemic, at least 90% of patients must be correctly identified and have access to appropriate treatment, and a cure rate of 90% must be achieved[4]. To increase detection and prevent delayed diagnosis, rapid molecular tests must be conducted in all suspected TB cases using GeneXpert or a similar test[5]. GeneXpert uses real-time PCR, which not only offers significantly greater sensitivity than sputum smear microscopy in the initial TB diagnosis, but also detects resistance to rifampicin in the same process. What is more, the entire test takes less than 2 hours[6].

Patients who test positive for RR-TB or MDR-TB must also undergo molecular testing for resistance to H, FQs and SLIs in order to offer the most appropriate treatment from the outset[7].

To improve the extremely low cure rate, patients with RR-TB/MDR-TB who are not resistant to FQs and/or SLIs should be administered a standardised and shortened (9-12-month) second-line treatment regimen[8]. Only these shortened regimens have achieved cure rates approaching 85-90%, compared with a mean cure rate of 52% for the conventional regimens of 21-24 months prescribed to date[2,8].

For MDR-TB patients who are also resistant to FQs, SLIs or both (XDR-TB), personalised regimens comprising at least 4 new drugs not previously administered to the patient must be prescribed[1]. Where possible, these should include the potent drug linezolid and the new drugs bedaquiline and delamanid, which have already been approved by the WHO[8]. These 3 drugs, together with other agents like carbapenems (imipenem, meropenem, ertapenem) and clofazimine[9], are successfully curing the vast majority of XDR-TB patients.

Although the current MDR-TB situation worldwide is a cause for grave concern, notable diagnostic and therapeutic advances have been made in the past 5-10 years that have significantly contributed to earlier diagnosis and higher cure rates for this disease subtype.

References

1. Caminero JA, Van Deun A, Fujiwara PI, Monedero I, Chiang CY, Rieder HL, et al. Guidelines for clinical and operational management of drug-resistant tuberculosis. Paris: International Union Against Tuberculosis and Lung Disease; 2013.
2. Organization WH. Global tuberculosis report 2016. World Health Organization Document. 2016;WHO/HTM/TB/2016;13:1–204.
3. García-García JM, Blanquer R, Rodrigo T, Caylà JA, Caminero JA, Vidal R, et al. Social, clinical and microbiological differential characteristics of tuberculosis among immigrants in Spain. PLoS ONE. 2011;6(1):e16272:doi:10.1371/journal.pone.0016272.
4. World Health Organization. Implementing the End TB Strategy: the essentials. World Health Organization Document. 2015;WHO/HTM/TB/2015;31:1–113.
5. Caminero JA MG. Automated Digital Microscopy in New Tuberculosis Diagnostic Algorithms. Can It Boost Case Finding? Am J Respir Crit Care Med. 2015;191(12):1352–3.
6. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. World Health Organization Document. 2013;WHO/HTM/TB/2013;16:1–79.
7. World Health Organization. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs. Policy guidance. World Health Organization Document. 2016;WHO/HTM/TB/2016.07.
8. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update. World Health Organization Document. 2016;WHO/HTM/TB/2016.04:1–59.
9. Caminero JA, Scardigli A. Classification of antituberculosis drugs: a new proposal based on the most recent evidence. Eur Respir J. 2015;46:887–93.

EditorialRespira

Monografías de Archivos de Bronconeumología

Ventilatory pump failure

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INTRODUCTION

$PaCO_2$ is strictly regulated in humans. Unlike PaO_2 and all other pulmonary function tests that decline with age, $PaCO_2$ remains constant throughout a person's life. This means that any sustained deviation in $PaCO_2$ levels represents a significant change in homeostasis[1].

Various anatomical and functional units may be grouped under the term respiratory pump. Its main function is to maintain $PaCO_2$ within very narrow limits. It is composed of structures ranging from the cerebral cortex to the respiratory muscles. Numerous clinical conditions involving these structures could lead to respiratory pump failure, which is characterised by hypercapnia[2]. According to the $PaCO_2$ equation, $PaCO_2$ increases as VCO_2 increases and/or VA decreases. It is not difficult to conceive of factors that could modify these two variables[3].

The importance of the respiratory pump has been known for decades. A series of studies opened the door to a significant number of basic, applied and clinical projects. The following is a review of some of these studies.

VENTILATION MONITORING

Until the middle of the 1970s, output of the respiratory centres was assessed by ventilation. However, this only reflected respiratory centre activity in normal subjects. In patients with mechanical limitation, ventilation may not reflect the output of the respiratory centres. This serious issue was resolved by Whitelaw, Derenne and Milic-Emili[4]. The simple measurement of mouth occlusion pressure in the first 0.1 seconds (P0.1 sec.) was postulated as "an index of the output of the respiratory centres that only depends on neuronal discharge and the contraction effectiveness of the respiratory muscles. It can be easily obtained, it is simple, non-invasive and could be a useful tool for both clinical and physiological studies". A search of the PubMed database using MeSH saw a sharp rise (25 articles/year) in the number of papers with the key words *control of breathing* and *occlusion pressure* from 1975 onwards.

Since then, the body of information on ventilation monitoring has focused on various areas – respiration and progression, rhythmicity, chemosensitivity and plasticity, neurotransmitters, cortical and subcortical involvement in dyspnoea, functional neuroimaging and the genetics of hypoventilation – until an understanding of the complexity of the respiratory system was attained and models based on the theoretical framework that proves chaos theory were implemented. In this light, two authors deserve a mention: MN Fiamma wrote: "In humans, lung ventilation exhibits breath-to-breath variability and dynamics that are nonlinear, complex, sensitive to initial conditions, unpredictable in the long-term, and chaotic"[5]. In line with this statement, Macklem challenged the medical community with a concept that was developed according to which "The disease is probably the result of being too close or too far from the thermodynamic equilibrium... Our complex physiology fluctuates and this variability is the spice of life... Variability is synonymous with health and rigidity is synonymous with disease"[6].

RESPIRATORY MUSCLES

Another milestone in our understanding of the respiratory pump took place in 1977 and concerned the respiratory muscles. Until that time, interest in these muscles had been limited to basic physiology. Roussos and Mackem successfully produced diaphragmatic fatigue using inspiratory resistances. This finding led to the hypothesis that "when the energy consumption of the respiratory muscles exceeds a critical level, fatigue should develop. This may be a mechanism of respiratory failure in a variety of lung diseases"[7]. They used 3 volunteers, 2 of which were the authors themselves, and the study probably would not have passed current EBM standards. However, it cannot be denied that this publication inspired clinicians' interest in the respiratory muscles and they began to be considered in patients with increased respiratory loads and/or respiratory muscle weakness, in patients with respiratory failure and those

weaned from mechanical ventilation. Approximately 180 articles per year featuring the term *respiratory muscles* in the title were recorded on the PubMed database using MeSH (an increase of almost 180%). However, the combination *respiratory muscles* + *critical care* only retrieved around 20 publications per year.

Subsequently, the body of information on the respiratory muscles comprised a variety of areas: Respiratory muscle dysfunction (fatigue, weakness, muscle injury, mechanical disadvantage), limited respiratory muscle functionality, concept of respiratory load vs respiratory muscle capacity, interaction with the patient (respiratory pump) – respirator, the molecular basis of response to respiratory loads and the development of non-invasive methods to assess diaphragm function.

At least 2 extremely influential articles were published in 1982, giving rise to more than 400 publications per year on the subject of *respiratory muscles*. Bellemare and Grassino defined the force reserve of the diaphragm according to the pressure swing developed and the timing of contraction. This gave rise to the classic Bellemare and Grassino diagram[8] or tension-time index of the diaphragm (TTdi). Rather than the TTdi just offering a load tolerance time, the authors hypothesised about the concept of respiratory muscle fatigue. They were aware of the studies conducted in the early twentieth century on non-respiratory muscle fatigue and hypothesised that "something similar" should happen to the respiratory muscles in humans. The Ti/Ttot and Pdi/Pdimax allows for many combinations and may result in an equation that is difficult to solve. However, Bellemare and Grassino found the equilateral hyperbolic function. It is clear that they knew what they were looking for.

The other article was by Cohen et al. They were the first to report clinical manifestations of inspiratory muscle fatigue in humans weaned from mechanical ventilation[9]. The respiratory pump had arrived on the scene of intensive care units.

These 2 publications paved the way for the force reserve of the diaphragm to be characterised in patients with COPD[10], followed by its application in intensive care[11,12]. They described "the tension-time index and the Fr/Vt as the major physiopathological determinants of the success or failure of weaning". As recently as 2009, Carlucci et al. conducted a study on tracheostomy patients at Weaning Centres, using TTdi in successful and failed weaning attempts in the same patients[13]. The authors concluded that "The recovery of an inadequate inspiratory muscle force could be the major determinant of 'late' weaning success, since this allows the patients to breathe far below the diaphragm fatigue threshold".

The authors Tobin, Laghi and Jubran have helped further our understanding of the respiratory pump in patients in intensive care, primarily respiratory pump failure, ventilatory support and weaning[14], thus improving on the relative lack of information of the past 20 years.

THE CONCEPT OF BALANCE BETWEEN ENERGY INPUT AND EXPENDITURE AND BETWEEN RESPIRATORY LOAD AND CAPACITY

The balance between energy input and expenditure, and between respiratory load and capacity, as well as certain features of diaphragmatic circulation are factors that underlie the aforementioned publications. An increased respiratory load refers to any lung, chest or cardiovascular condition that leads to increased energy expenditure. A reduced respiratory capacity refers to any condition that involves respiratory muscle weakness, reduced respiratory centre output or neuromuscular junction transmission defects[15]. Diaphragmatic circulation is 6 times more efficient per gram of tissue than the circle of Willis. The respiratory muscles recover from fatigue approximately 10 times quicker than leg or arm muscles. It seems that evolution developed in such a way as to equip the diaphragm rather than the brain with blood circulation with a wide margin of energy input versus energy expenditure. This concept of energy input and expenditure and respiratory load and capacity is central to planning treatment strategies, with the objective of improving the input/expenditure ratio, reducing the respiratory load and increasing the capacity of the respiratory muscles.

FROM MACROSCOPIC PHYSIOLOGY TO MOLECULAR AND TRANSLATIONAL PHYSIOLOGY

From the end of the twentieth century, "macroscopic" physiology started to give way to molecular physiology and translational physiology, and this has continued into the twenty-first century. The inspiratory resistive load is an immune challenge. Oxidative stress triggers an inflammatory response (cytokines, lymphocytes). The cytokines originate in the diaphragm and may either cause muscle damage or repair. They can also lead to weakness and cachexia. The resistive load releases glucose and fatty acids, as well as ACTH and glucocorticoids in the adrenal axis. Finally, beta-endorphins reduce the activity of the respiratory muscles leading to rapid and superficial respiration[16]. These studies are furthering our understanding of the macroscopic physiology and paving the way for therapeutic pharmacological interventions.

VENTILATORY PUMP ASSESSMENT

Numerous cases highlighting the signs and symptoms of respiratory pump failure can be found in the literature, particularly in patients with neuromuscular disease. There are numerous different tests available to assess the condition, each with different and complementary approaches. They include: chest X-ray, fluoroscopy, lying and sitting FVC, maximum mouth pressures (PImax and PEmax), maximum Pdi, intragastric pressure with nasogastric tube (Pga), phrenic latency, occlusion pressure (P0.1) and diaphragm ultrasound[17,18].

Of all these methods listed, articles concerning diaphragm ultrasound have increased significantly since 2010 (PubMed database using MeSH *diaphragm* + *ultrasonography*). This fact warrants special mention. It is a non-invasive, non-ionising and real-time method. It facilitates diaphragm assessment in different settings – outpatient, pulmonary laboratory and intensive care – and under different conditions. It assesses diaphragm inspiratory thickness in the zone of apposition and measures the shortening and relaxing speed of the diaphragm, both of which are related to onset of diaphragm fatigue. Although the technique has yet to be properly standardised, it is potentially useful for studying severe diaphragm dysfunction in clinical practice[19,20].

CONCLUSIONS

This was a review of the articles that contributed to furthering our understanding of the respiratory pump. Thanks to their findings over the past 40 years, our understanding of the physiology and physiopathology of respiratory pump failure today is fairly comprehensive. However,

given that much of our knowledge concerning patients with ventilatory failure and repeated weaning failures can still be extrapolated today to other similar situations, these aspects should be further studied by specific trials. Our understanding of "macroscopic" physiology is improving thanks to basic and applied studies and through translational medicine. The diaphragm ultrasound technique has shown promising results in the structural and functional assessment of the diaphragm. Recent findings are of physiopathological interest and could be useful in a clinical/healthcare context and to improve our knowledge of respiratory pump failure. All therapeutic regimens should consider the input/expenditure and load/capacity ratios. It is hoped that our knowledge of molecular physiology will lead to the development of pharmacological regimens.

References

1. De Vito EL. Alteraciones respiratorias del estado ácido-base. En: SATI (Sociedad Argentina de Terapia Intensiva). Terapia intensiva. 5ª ed. Argentina: Editorial Médica Panamericana, 2015;X:4.
2. Benditt JO. The neuromuscular respiratory system: physiology, pathophysiology, and a respiratory care approach to patients. Respir Care. 2006 Aug;51(8):829-37;discussion 837-9.
3. Antonaglia C, Garuti G, Torregiani C. Management of patients with neuromuscular disorders and acute respiratory failure. Shortness of Breath 2014;3:181-9.
4. Whitelaw WA, Derenne JP, Milic-Emili J. Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol. 1975 Mar;23(2):181-99.
5. Fiamma MN[1], Straus C, Thibault S, Wysocki M, Baconnier P, Similowski T. Effects of hypercapnia and hypocapnia on ventilatory variability and the chaotic dynamics of ventilatory flow in humans. Am J Physiol Regul Integr Comp Physiol 2007 May;292(5):R1985-93.
6. Macklem PT. A matter of life and death. Rev Mal Respir. 2002 Apr;19(2 Pt1):135-9.
7. Roussos CS, Macklem PT. Diaphragmatic fatigue in man. J Appl Physiol Respir Environ Exerc Physiol. 1977 Aug;43(2):189-97.
8. Bellemare F, Grassino A. Evaluation of human diaphragm fatigue. J Appl Physiol Respir Environ Exerc Physiol. 1982 Nov;53(5):1196-206.
9. Cohen MV, Yipintsoi T, Scheuer J. Coronary collateral stimulation by exercise in dogs with stenotic coronary arteries. J Appl Physiol Respir Environ Exerc Physiol. 1982 Mar;52(3):664-71.
10. Bellemare F, Grassino A. Force reserve of the diaphragm in patients with chronic obstructive pulmonary disease. J Appl Physiol Respir Environ Exerc Physiol. 1983 Jul;55(1 Pt 1):8-15.
11. Jubran A[1], Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med. 1997 Mar;155(3):906-15.
12. Vassilakopoulos T, Zakynthinos S, Roussos C. The tension-time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. Am J Respir Crit Care Med. 1998 Aug;158(2):378-85.
13. Carlucci A, Ceriana P, Prinianakis G, Fanfulla F, Colombo R, Nava S. Determinants of weaning success in patients with prolonged mechanical ventilation. Crit Care. 2009;13(3):R97. doi:10.1186/cc7927.
14. Tobin MJ[1], Laghi F, Jubran A. Ventilatory failure, ventilator support, and ventilator weaning. Compr Physiol. 2012 Oct;2(4):2871-921.
15. McConville JF, Kress JP. Weaning patients from the ventilator. N Engl J Med. 2012 Dec 6;367(23):2233-9.
16. Vassilakopoulos T, Roussos C, Zakynthinos S. The immune response to resistive breathing. Eur Respir J. 2004 Dec;24(6):1033-43.
17. Flaminiano LE1, Celli BR. Respiratory muscle testing. Clin Chest Med. 2001 Dec;22(4):661-77.
18. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002 Aug 15;166(4):518-624.
19. Orozco-Levi M, Gayete A, Rodríguez C, Ramírez-Sarmiento A, Méndez R, Tous F, Vollmer I, Gea J, Molina L. Non-invasive functional evaluation of the reserve in fatigue and the diaphragm structure using transthoracic echography in B and M modes, Arch Bronconeumol. 2010 Nov;46(11):571-9.
20. Sferrazza Papa GF1, Pellegrino GM, Di Marco F, Imeri G, Brochard L, Goligher E, Centanni S. A Review of the Ultrasound Assessment of Diaphragmatic Function in Clinical Practice. Respiration. 2016;91(5):403-11.

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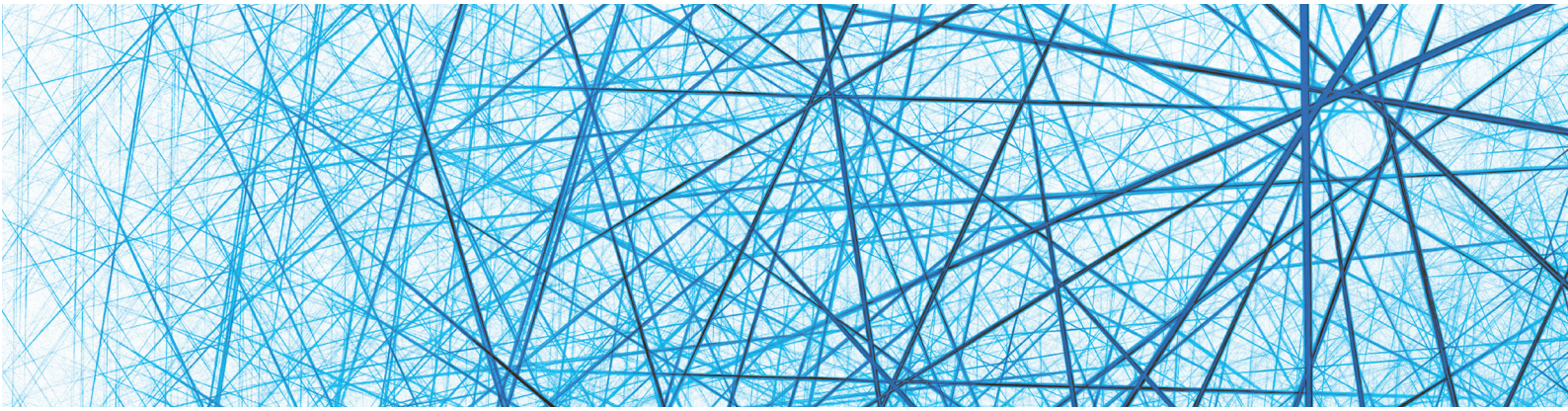

ABSTRACTS

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EditorialRespira

Monografías de Archivos de Bronconeumología

Safety of transbronchial lung cryobiopsy in mechanically ventilated patients in critical care. Multicenter study

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BACKGROUND

Diagnosis of diffuse lung infiltrates (DLI) in acute mechanically ventilated (MV) patients is challenging. Obtaining lung samples is useful when conventional methods fail, but the best method is not established. Transbronchial lung cryobiopsy (TBLC) gets bigger samples and increases diagnostic yield of conventional method in interstitial lung disease, but it has not been tested in MV patients.

AIMS

To analyze the feasibility, safety and potential role of TBLC in the diagnosis of DLI in MV patients.

METHODS

Multicenter and prospective study. We included MV patients with non-diagnosed DLI with conventional methods. Oro-tracheal tube (OTT) was changed to a Bronchoflex Rüsh® that allowed the use of a haemostatic balloon. It was allocated in the bronchi previous to obtaining TBLC with 2.4 mm cryoprobe through a flexible bronchoscope.

RESULTS

We performed 49 biopsies in 17 patients (median age 65 [51-76] and PaFi 62.3 [118.9–264.9]). All samples were valid for histological analysis, allowing a specific diagnostic pattern in 47% patients, but promoting changes in therapeutic management in 88.2% cases. Change of OTT was associated to transitory adverse events. One patient had a massive bleeding related to procedure, requiring selective intubation less than 24h. No pneumothorax was recorded. 10 patients (58.8%) died, but none were related to the TBLC.

CONCLUSIONS

TBLC is a feasible technique to obtain lung biopsies in MV patients. Pathological results had a direct clinical impact in the management of undiagnosed pulmonary infiltrates in MV patients. Further research is needed to establish risk-benefit and diagnostic yield in these patients.

EditorialRespira

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Asthma with hypersecretion-associated gene for cystic fibrosis. Clinical, inflammatory and genetics characterization

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INTRODUCTION

Asthma with bronchial hypersecretion is a variant of the disease characterized insufficiently. Some authors have proposed a possible relation with to be carrier of genetic variants in the CFTR (Cystic fibrosis transmembrane conductance regulator) gene.

OBJECTIVES

1) Determine the presence of genetic variants of the CFTR gene in asthmatics patients with or without bronchial hypersecretion. 2) To define the demographic, clinical and functional characteristics of asthmatics patients with or without bronchial hypersecretion.

METHODS

This is a cross-comparative multicenter study. A total of 100 asthmatic patients, non-smokers and without bronchiectasis were included. All patients underwent the following: induced sputum, spirometry, fractional exhaled nitric oxide, prick test, total IgE and blood albumin. The level of asthma control was determined by the asthma control test questionnaire and quality of life was assessed by the MiniAQLQ questionnaire. The genetic study is performed using massive sequencing using a Miseq team Illumina platform.

RESULTS

Compared to the non-hypersecretory group, hypersecretory asthmatics patients were older; had greater severity; increased bronchial obstruction; less control of asthma; a higher proportion of asthma with negative prick test; lower levels of IgE (see Table 1). Compared to the non-hypersecretory group, hypersecretory asthmatics patients had a greater presence of the polymorphism c.1680-870T> (78.94% vs 59.32% in the largest alleles; p=0.036).

CONCLUSION

Asthmatics patients with bronchial hypersecretion have a more severe and uncontrolled disease, as well as a non-allergic inflammatory phenotype. Also, asthma with bronchial hypersecretion is associated with a polymorphism in the CFTR gene specifically to c.1680-870T> A.

Grupo Emergente de Asma de la SEPAR. This study has been funded by grant of SEPAR 2014 and AstraZeneca.

EditorialRespira

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Benefit of virtual navigation in the diagnostic yield of ultrafine bronchoscopy for the study of lung lesions

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INTRODUCTION

The ultrathin bronchoscopy can reach the tenth bronchial generation by endobronchial way, allowing access to pulmonary lesions beyond the reach of conventional bronchoscopes. However, from the fourth generation, the path to the target is often difficult to determine. Virtual bronchoscopic navigation could be a helpful tool in such exploration.

HYPOTHESIS

The ultrathin virtual bronchoscopy guided navigation (BUNV) is superior to that performed without navigation (BUSNV).

OBJECTIVES

To compare the diagnostic performance of both techniques and determine whether there are differences in the total scan time requirement and complementary diagnostic procedures.

METHODOLOGY

Prospective study of cases and controls matched 1: 2 by lesion size, bronchus sign, location of injury, sex and prevalence of cancer in a tertiary hospital.

RESULTS

21 lesions in BUNV group and 42 lesions were included BUSNV group. In both groups, 90.47% of the lesions were lower than 3 cm. The diagnostic performance for virtual navigation group was 75%, while in control group (BUSNV) was 43.9% (p = 0.029). Complementary diagnostic procedures were necessary in 52% of the patients in the control group, while in the virtual navigation group only 14.28% (p = 0.001). There were no differences in total scan time.

CONCLUSIONS

The virtual navigation is an instrumental technique that increases the diagnostic yield of ultrafine bronchoscopy in the study of pulmonary nodule.

EditorialRespira

Monografías de Archivos de Bronconeumología

New biomarker in intersticial lung disease

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INTRODUCTION

Serum biomarkers may be identity to explain the pathogenesis of interstitials diseases (ILD). The advanced glycation end-products (AGEs) are a group of products of non-enzymatic glycation and oxidation of proteins, nucleic acids and lipids that physiologically accumulate in tissues and excessive accumulation of extracellular matrix. The aim is to determine the peripheral blood levels of this biomarker and establish their relationship with the ILD.

METHODS

A blood sample from 35 subjects diagnosed with ILD and 30 healthy controls were processed. In addition clinical variables were collected.

RESULTS

The groups were homogeneous. AGE levels were elevated in patients (p = 0.038). In idiopathic pulmonary fibrosis (FPI) the level in peripheral blood was 2728.93, in Connective Tissue Disease associated Interstitial Lung Disease (ILD-CTD) 3917.14 and 1918.5 in healthy subjects. The area under the curve (AUC) for AGE in FPI was 0.78 with a cut-off value of 2370. The sensitivity (S) of AGEs to differentiate FPI was 71.43 with a specificity (E) of 80%. AGEs for ILD-CTD has an AUC of 0.96, with a cut-off of 2384.96, S= 85.71% and E = 80% (95% CI).

CONCLUSIONS

AGE is involved in the pathogenesis of ILD. It can be considered a biomarker for the diagnosis of ILD. This is the first work that also allows distinguishing FPI and ILD-CTD using a biomarker. A determination of AGE allows early diagnosis of patients with CTD-ILD contributing to early treatment and may improve the prognosis. AGE may be a potential therapeutic target.

EditorialRespira

Monografías de Archivos de Bronconeumología

Differences in the blood transcriptome between COPD patients and healthy subjects

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INTRODUCTION

COPD is a highly prevalent and heterogeneous disorder.

OBJECTIVE

To compare the blood transcriptome of COPD patients with that of healthy subjects.

METHODS

Blood samples from a subset of 40 patients and 20 healthy volunteers were obtained, and the RNA was extracted and subsequently sequenced (NextSeq, 3 runs with 400 M reads/run). Differential expression analysis between COPD patients and controls was done using a standard bioinformatics pipeline.

RESULTS

25,221 gene expression profiles were obtained, and differential expression analysis revealed that COPD patients showed a significant overexpression of 26 genes, standing out among them DSEL (related to carcinogenesis and fibrosis, Δ98%), LRRN3 (a marker of exposure to tobacco, Δ96%), TSPAN16 and CD8A (cell activation/proliferation and cytotoxic action of T lymphocytes, respectively, Δ46% both), and PER1 (regulator of circadian rhythms in cells, possibly involved in cancer, Δ55%). Significant underexpression was observed in 23 more genes, including CD38 (Δ41%, a regulator of innate and adaptive immunity). Functional analysis identified an enrichment of differentially expressed genes, mainly in immune pathways (e.g. that mediated by B cells, OR 29), as well as in genes linked to iron transport (OR 21.3) or intracellular signaling (cAMP, OR 12.4).

CONCLUSION

There are significant gene expression changes in COPD patients, which singularly involve immune pathways. This study shows that a uniform exploration of transcriptomic changes can help in a better understanding of the mechanisms and/or effects of COPD, also contributing to a better characterization of patients, and eventually to the design of new diagnostic and therapeutic strategies.

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EditorialRespira

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High LTBI positivity rates due to methotrexate. False positives?

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INTRODUCTION

Clinical studies have associated the use of TNF blockers with progression from latent tuberculosis infection (LTBI) to tuberculosis (TB) disease. Patients with Rheumathoid Arthritis (RA) have far higher percentages of positive Tuberculin Skin Test (TST) results compared with the Interferon Gamma Release assays (IGRA).

OBJECTIVE

To determine the influence of Methotrexate (MTX) used in patients with rheumatic diseases on the performance of LTBI screening tests.

MATERIAL AND METHODS

LTBI diagnosis was based on a history of contact with an active TB, chest X Ray indicative of LTBI, a positive TST, and/or a positive IGRA. Determination of T-cell subpopulations was also performed. To verify the results peripheral blood mononuclear cells were isolated. Cultures were performed in RPMI 1640 medium. Cells were incubated at 37°C under 5% carbon dioxide.

RESULTS

Between April 29, 2013 and March 29, 2016, 393 patients were prospectively included. TST was positive for 22.2% ankylosing spondylitis (SpA) patients, for 25% rheumatoid arthritis (RA) patients and 35.7% of Psoriatic Arthritis (PA) patients. QFT positive results were 15.6% (SpA), 20% (RA), 19% (PA). T.SPOT TB positive results were: 13.5% (SpA), 14.2% (RA), 15.3% (PA).

MAIN FINDINGS

1. MTX appears to be related to a high number of TST positive results in patients with rheumatic diseases.
2. T-lymphocytes from MTX treated patients are higher IFN- γ producers at low doses of anti-CD3 than from MTX untreated patients.

EditorialRespira

Monografías de Archivos de Bronconeumología

Effectiveness of personalized physical training intervention (preHABilitation) in high-risk patients undergoing major abdominal surgery: randomized controlled trial

Authors

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BACKGROUND

Based on the notion that preoperative functional reserve and cardiopulmonary fitness are predictors of postoperative morbidity, *prehabilitation*, defined as the process of enhancing the functional capacity, results a highly promising preventive intervention to improve the surgical outcome.

OBJECTIVE

To evaluate the effectiveness of a preoperative personalized exercise training intervention (preHAB) in high-risk patients undergoing major abdominal surgery on postoperative outcomes.

METHODS

Single-blind randomized control trial. 144 high risk surgical patients (i.e., >70 yr-old and / or ASA III-IV) planned for elective major abdominal surgery were randomized to preHAB program or conventional preoperative care. Primary outcome measure was the incidence of postoperative complications.

RESULTS

125 patients (preHAB group n=62 and control group n=63) were included in the analysis. At program discharge (mean duration 6 weeks), preHAB group showed an improvement of 135 (218) % in endurance time (p<0.001) meanwhile the control group remained unchanged. Complications rate was substantially lower in the preHAB group (31% versus 62%, p=0.001). The preHAB intervention was showed as a protective factor for postoperative complications: RR 0·5, 95% CI (0·3-0·8). Patients in the control group showed a trend for a longer stay in the intensive care unit [4 (13) vs. 1 (2) days for control and intervention group respectively; p=0.084] and hospital length of stay [13 (21) vs. 8 (8) days for control and intervention group respectively; p=0.117] although no significant difference showed up.

MAIN FINDINGS

A preHAB program is effective for reducing morbidity rates in high risk surgical patients after major abdominal surgery.

EditorialRespira

Monografías de Archivos de Bronconeumología

Time to blood culture positivity as a predictor of clinical outcomes and severity in adults with bacteremic pneumococcal pneumonia

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BACKGROUND

The time to positivity of blood culture (TTP) of patients with bacteremia has been previously explored as a marker of poor clinical outcome. However, the association of TTP with the clinical outcome and severity of pneumococcal bacteremic pneumonia in adults has never been studied.

METHODS

Prospective observational study carried out in 278 hospitalized adult CAP patients with positive blood culture for *Streptococcus pneumoniae* during 2009 to 2011.

RESULTS

A total of 278 cases of bacteremic pneumococcal pneumonia were analyzed, median age 62 (46; 79) years, 167 (60%) of the patients were male. Fifty-one percent of the cases had PSI IV-V. 21 (8%) died within 30-days after admission. The analysis of the TTP demonstrated that the first quartile of the TTP (9.2h) was the best cut-off for differentiating 2 groups of patients at risk, early (TTP <9.2 h) and late (TTP ≥9.2 h) detection groups. Early TTP was associated with a statistically significant risk of mechanical ventilation (MV) (OR 2.2); longer length of stay (LOS) (OR 6.7); higher in-hospital mortality (OR 3.7) and 30-day mortality (OR 3.0). Logistic regression, adjusted for age, sex, comorbidities, PSI , revealed early TTP as independently associated with high risk of MV (OR 4.6; 95% CI 1.6–13.0), longer LOS (OR 5.2; 95% CI 1.8–8.5) and higher in-hospital mortality (OR 5.3; 95% CI 1.5 – 18.5)

CONCLUSION

TTP is inversely related with the bacterial load in the blood. In line with this fact, our results demonstrate that TTP is an easy to obtain surrogate marker of pneumococcal pneumonia severity and a good predictor of its outcome.

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Therapeutic effects of soluble guanylate cyclase (SGC) stimulation on pulmonary hemodynamics and emphysema development in guinea pigs chronically exposed to cigarette smoke

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BACKGROUND

We have previously shown that stimulation of sGC is able to prevent both pulmonary vascular remodeling and emphysema in a guinea pig model of chronic obstructive pulmonary disease (COPD). Therapeutic effects of the drug in experimental COPD have not been assessed yet. Consequently, the aim of our study was to evaluate in a therapeutic setting the effects of the sGC-stimulator BAY 41-2272 in guinea pigs chronically exposed to cigarette smoke (CS).

METHODS

Guinea pigs exposed to CS for 3 months continued CS exposure [CS group, n=15] or were sham-exposed during 3 additional months [Ex-CS group, n=15]. A control group of animals was sham-exposed for 6 months [Sham group, n=12]. Half of the animals of each group received BAY 41-2272 (6 mg/Kg/day during the last 3 months) and the rest an adequate amount of vehicle. At the end of the study, airway resistance (enhanced pause, Penh), pulmonary artery pressure (PAP), right ventricular hypertrophy (Fulton-Index, RVH) and emphysema (mean linear intersept, MLI) were analyzed.

Guinea pigs exposed to CS for 6 months showed a higher Fulton-Index and emphysema [p<0.001 each] and a trend to increased PAP values. In this group, treatment with BAY 41-2272 improved the Fulton-Index [p=0.03] and MLI [p=0.029] significantly, whereas PAP and Penh remained unchanged. In the Ex-CS group, the Fulton-Index did not differ from controls, whereas the MLI was higher [p=0.006] and similar to CS-exposed animals. In the Ex-CS group treated with BAY 41-2272, the MLI was lower [p=0.019] than in the CS-group and similar to controls.

CONCLUSION

In guinea pigs exposed to CS, smoking cessation reduces RVH, but does not recover the extent of emphysema. Therapeutic intervention with a sGC-stimulator decreases the MLI in animals who stopped smoking and recovers RVH and the MLI in those who continue smoking. These results highlight the significant impact of sGC-stimulators on emphysema development in animals exposed to CS.

Results:	Sham + Vehicle	Sham + BAY 41-2272	Ex-CS + Vehicle	Ex-CS + BAY 41-2272	CS + Vehicle	CS + BAY 41-2272
Penh (AUC)	5.05 ± 0.84	4.93 ± 0.59	6.24 ± 1.04	5.52 ± 1.18	6.02 ± 1.67	6.67 ± 0.98
PAP (mmHg)	8.82 ± 1.46	9.58 ± 1.76	8.18 ± 2.22	7.71 ± 2.11	10.22 ± 1.69	10.25 ± 2.26
Fulton-Index (RV/LV+Septum)	0.28 ± 0.03	0.27 ± 0.02	0.31 ± 0.02	0.29 ± 0.03	0.34 ± 0.03*	0.30 ± 0.03†
MLI (µm)	71.45 ± 6.83	64.21 ± 6.61	84.75 ± 10.04*	74.46 ± 5.43◊	87.90 ± 6.57*	78.39 ± 8.75†

p < 0.05: * vs. Sham+Vehicle; ◊ vs. Ex-CS+Vehicle; † vs. CS+Vehicle; all data are represented as mean ± SD. Statistical differences were analyzed by means of 2-way ANOVA with Holm-Sidak post-hoc test.

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EditorialRespira

Monografías de Archivos de Bronconeumología

COPD incidence in subjects with risk factors, chronic respiratory symptoms and normal spirometry: The PLATINO study

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BACKGROUND

The GOLD-2001 staging system establishes the stage at risk for developing COPD (GOLD 0), however this was later discarded for not having evidence that these subjects were more likely to develop COPD. Despite this, the controversy persists about the factors that help identify susceptible subjects. The aim of this study is to determine the factors associated with COPD incidence in the PLATINO follow-up study.

METHODS

The COPD incidence rate was determined per 1,000 subjects with spirometric criteria (post-bronchodilator $FEV_1/FVC<0.7$), adjusted by the follow-up time. Dyspnea, bronchial hypersecretion was self-reported and smoking by pack-years.

RESULTS

1,797 subjects completed the follow-up and 154 incident cases were identified. The incidence rates in smokers ≥10 and ≥20 pack-year were 16 cases/year (IRR: 1.54; $p<0.05$) and 19.9 cases/year (IRR: 1.74; $p<0.05$), respectively. The incidence rates in patients with bronchial hypersecretion and dyspnea were 14.8 cases/year (IRR: 0.87; $p>0.05$) and 17.1 cases/year (IRR: 1.13; $p>0.05$), respectively. There was not increment in the incidence rate by associating the symptoms to smoking history (Bronchial hypersecretion+smoking: 15.3 cases, IRR: 1.56, $p>0.05$; dyspnea+smoking: 17.5 cases, IRR: 1.21, $p>0.05$; bronchial hypersecretion+dyspnea+smoking: 9.6 cases, IRR: 1.69, $p>0.05$). Other factors related to COPD incidence were: ≥60 years, BMI <18.5 kg/m^2, low education and baseline FEV_1 80-90%.

CONCLUSIONS

Smoking history >10 packs/year, regardless of the presence of symptoms is the main factor associated with the COPD incidence in the PLATINO study. Prospective studies are needed analyzing other outcomes and identify biomarkers that help better identify this group of patients.

EditorialRespira

Monografías de Archivos de Bronconeumología

Multi-level differential network analysis of COPD exacerbations: The ecos study

Authors

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BACKGROUND

Patients with chronic obstructive pulmonary disease often suffer episodes of exacerbation (ECOPD) that impact negatively the course and prognosis of their disease. ECOPD are heterogeneous events of unclear pathobiology and non-specific diagnosis (increase in symptoms). Network analysis is a novel research approach that can help unraveling complex biological systems. We hypothesized that the comparison of multi-level (i.e., clinical, physiological, biological, imaging and microbiological) correlation networks during ECOPD and at clinical recovery can yield useful patho-biologic information.

METHODS

We studied 86 patients hospitalized because ECOPD recruited in a multicenter study in Spain. Patients were extensively characterized phenotypically and studied also during clinical stability. We used multi-level, differential, correlation network analysis to compare both conditions.

RESULTS

(1) Episodes of ECOPD are characterized by disruption of the network correlation observed during clinical stability; (2) a panel of biomarkers that include increases in dyspnea, circulating neutrophils and C-reactive protein levels has a high predictive value for the diagnosis of ECOPD (AUC = 0.97); and, (3) cluster analysis of network differences between ECOPD and clinical stability identified three different clusters.

CONCLUSIONS

(1) ECOPD disrupt network homeokinesis observed during clinical stability, likely reducing system control and resilience; (2) a panel of biomarkers commonly measured in the clinic has high predictive value for the objective diagnosis of ECOPD; and, (3) ECOPD episodes are heterogeneous events which likely require individualized (i.e., precise) management strategies. The latter two conclusions require validation in prospective studies.

EditorialRespira

Monografías de Archivos de Bronconeumología

EGFR and KRAS mutations are also present in non-tumoral lung tissue of patients with resected adenocarcinoma

Authors

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INTRODUCTION

Pulmonary adenocarcinoma (PA) is a tumor that develops from the airways (club-cell or type-II pneumocyte differentiation). Genetic alterations that may have implications for prognosis and treatment are frequently detected, and molecular testing is routinely performed in patients with advanced disease but not in patients undergoing surgery. Even when the surgery is performed, up to 30% of patients exhibit disease progression.

OBJECTIVE

To identify whether the most prevalent mutations in patients with PA, are also observed in the normal lung tissue and to assess if these molecular alterations have prognosis implications.

MATERIALS

We performed genomic testing for driver mutations to patients with PA who were candidates for curative surgery (2009-15). In patients with EGFR-KRAS mutation in tumor, we carried out highly specific and sensitive Competitive Allele-Specific PCR (CastPCR) in normal parenchyma to explore the same mutations.

RESULTS

From the 625 patients identified, 169 (26.8%) were candidates for resection and 47 had KRAS-EGFR mutations. In 10 patients (21.3%) of the latter group we identified the same driver mutation in tumor and normal parenchyma (SDM). There were no differences between SDM and non-SDM groups in terms of lung function, preoperative TNM and the diagnosis-to-surgery time, but SDM patients presented a worse post-surgery TNM (nodal infiltration 30 vs 13.5%, $p<0.05$).

CONCLUSION

This is the first study demonstrating the presence of the same driver mutations in normal lung parenchyma of patients with lung cancer, and relating these mutations with worse postoperative outcomes. These findings may explain the pathophysiology of cancer progression in patients theoretically cured.

EditorialRespira

Monografías de Archivos de Bronconeumología

Impact of short-term low-dose vs. standard-dose varenicline therapy on the rate of smoking abstinence, treatment adherence and adverse effects

Authors

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AIMS

Varenicline is used in smoking cessation. The aims of the study were to test for differences in clinical practice between 1 mg and 0.5 mg (both twice daily during 8 weeks) in abstinence, adherence and side effects.

DESIGN

Open-label randomized parallel-group controlled trial with 1-year follow-up. All those randomized were included in the final sample using an intention-to-treat (ITT) approach.

SETTING

Stop-Smoking Clinic of the Virgen Macarena University Hospital in Seville, Spain.

PARTICIPANTS

Smokers (n=484) of which 59.5% were men with a mean age of 50.67 years-old and a smoking history of 37.5 pack-years, were randomized to 1mg (n=245) vs. 0.5mg (n=239) and received behavioural support, which consisted of a baseline visit and 6 follow-ups during 1 year.

MEASUREMENTS

The primary outcome was continuous self-reported abstinence over 1 year, with biochemical verification. The secondary outcomes were adherence and side effects. Also measured were baseline demographics, medical history and smoking characteristics.

FINDINGS

Abstinence rates at 1 year were 46.5% with 1mg vs. 46.4% with 0.5 mg (OR,0.997;95%CI,0.7-1.43;p=1.0). Treatment adherence was similar in both regimens (p=0.44). Side effects were reported in 19.3% of cases with 1mg vs. 12.1% with 0.5 mg, although with no significant differences between regimens (p=0.093).

CONCLUSIONS

In this single-center study, there is no difference in smoking cessation effectiveness between 1mg and 0.5 mg varenicline both twice daily for 8 weeks, with similar rates of abstinence, adherence and side effects.

EditorialRespira

Monografías de Archivos de Bronconeumología

Effects of intensive glucose lowering on pulmonary function. A case-control study in Type 2 diabetic patients

Authors

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INTRODUCTION

There is growing evidence suggesting a deleterious effect of type 2 diabetes (T2D) on lung function. However, only one previous study has showed how glycemic control improvement significantly reduces the number of nocturnal oxygen desaturation events. Now, we show data about the impact of 3-months glycemic intensification control on lung function.

MATERIALS AND METHODS

Prospective interventional study in 58 patients with T2D and no lung disease (59.2% men; age: 59.6±10.4 yrs.; T2D duration 11.8 ±6.2 yrs., BMI 30.8±6.6 kg/m^2, and HbA1c 9.7±1.5%). During a 3-months period, baseline spirometry was performed and the hypoglycemic treatment was modified, with priority given to therapies with less effect on weight reduction. At the end of this period, HbA1c and BMI decreased to 7.1±1.0% and 30.2±5.9 kg/m^2 ($p<0.001$ and $p=0.062$, respectively), and spirometry was repeated.

RESULTS

The percentage of patients with a restrictive pattern was reduced from 28.6% to 12.2% ($p<0.05$). In addition, absolute change in HbA1c was negatively correlated with increases on lung function parameters, particularly those related to small airways: FEF25-75% (r=-0.395, p=0.005), FEV_1/FVC (r=-0.375, p=0.008), and instantaneous forced expiratory flow 50% (FEF50%; r=-0.390, p=0.006). Finally, multivariate analysis showed that the decrease in HbA1c, but not in BMI, was independently associated with the increases in FEF25-75% (R^2=15.6%), FEV_1/FVC (R^2=14.1%), and FEF50% (R^2=15.2%).

CONCLUSION

This is the first clinical evidence of a positive effect of glycemic control improvement on lung function, and support the concept that the lung is a new target of diabetic complications.

EditorialRespira

Monografías de Archivos de Bronconeumología

Effectiveness of an intervention of urban training in patients with chronic obstructive

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INTRODUCTION

Reduced levels of physical activity (PA) have been consistently related to worse COPD prognosis. There is a need to test interventions that increase PA in COPD.

AIM

To assess the efficacy and effectiveness of the Urban Training (UT) intervention on PA level after 12 months of follow-up in COPD patients.

METHODS

Multicenter randomized controlled trial. 411 patients were recruited from 33 primary care centers and 5 tertiary hospitals from five Catalan municipalities. UT intervention (n=204) conducted in public spaces which used behavioral strategies by combining motivational interviewing, walking trails, pedometers, calendars, website, pamphlets, phone text messages, walking groups and call-center. Usual care group (n=207) received general PA recommendation. Main outcome was PA measured by accelerometer (steps/day), and secondary were COPD hospital admissions, exercise capacity, body composition, health-related quality of life, anxiety and depression after follow-up. Modified intention to treat (MITT) and per protocol (PP) analysis were performed (PP including only patients adherent to their corresponding intervention).

RESULTS

284 patients completed the 12 months follow-up assessment. In the MITT analysis, there was no difference between groups in PA (7807 steps/day in the usual care vs 7843 in the intervention group, p=0.943). However, a large difference was observed in the PP analysis (7807 vs 9100 steps/day respectively, p=0.035). There were no differences in secondary outcomes between groups in both analyses.

CONCLUSIONS

The UT intervention increased PA after 12 months of follow-up in adherent patients. UT may be a potentially feasible intervention for COPD patients because of itssimplicity and reduced burden.

EditorialRespira

Monografías de Archivos de Bronconeumología

Genetic susceptibility in COPD, more than AAT

Authors

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Smoking and exposure to smoke from burning biomass are environmental risk factors most clearly associated with developing COPD. Different studies have evaluated the association involving single nucleotide polymorphisms (SNPs) in the pathology. Given the extensive polymorphism and the large number of genes involved in possible biological mechanisms, the use of genomic platforms facilitates the identification of genetic variants involved in susceptibility and/or greater clinical severity of COPD.

The best-documented genetic factor is alpha-1 antitrypsin (AAT), encoded by the SERPINA1 gene. Among our findings, COPD-causing AAT deficiency risk alleles exist at a very low frequency among Mexican Mestizo population, these risk alleles are associated with poorer lung function measurements. (PMID: 25454901). We evaluated 1285 SNP of candidate genes using an Illumina GoldenGate genotyping microarray. COPD group was stratified by severity per GOLD, 3 SNPs in IL6R and one in ADAM19 were associated with a lower risk of suffering the most severe stages of the disease. rs2819096 in the SFTPD gene was associated with a higher risk of COPD GOLD III + IV (PMID: 27078193). Currently, we are evaluating microbiome among COPD secondary to wood smoke. Regarding to nicotine addiction, recently, we have found two SNPs in NRXN1 and two in CHRNA5 associated with cigarette consumption, while another in NRXN1 was associated with high nicotine addiction (PMID: 27355804). We proposed new hypotheses regarding the putative roles of miRNAs that influence the GABAergic and glutamatergic pathways in smoking addiction. By now, we are evaluating SNPs and VNTRs in DRD4 and HTR2A genes.

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