REVIEW ARTICLE

# The Archivos Archive, 2007: An Overview of Research Published in *Archivos de Bronconeumología*

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## Introduction

As was commented last year in a review of 2006 publications in *Archivos de Bronconeumología*,[1] the quality of original articles published that year was high, and that level was maintained in 2007. Moreover, this quality was once again reflected by the higher impact factor the journal achieved in 2007. When reporting on the scientific contribution of a piece of research, it is important to distinguish between quality, importance or relevance, and impact. Quality relates to how well a study is carried out (aspects such as originality, proper use of appropriate methodology, and study design); importance refers to the potential influence of the findings; and impact is a measure of the eventual repercussion of the research. In short, proper evaluation of research should take all of these 3 elements into account. This is clearly being done by the team at *Archivos de Bronconeumología*, since it could be said that the scientific quality of a journal begins to rise when the impact factor increases.[2]

As in the previous year, in 2007 a total of 59 original articles were published in *Archivos de Bronconeumología*. In this review, we have grouped the articles by subject matter, keeping as far as is possible to the format used in last year's review.

## Chronic Obstructive Pulmonary Disease

It is well known that skeletal muscle dysfunction is common in patients with chronic obstructive pulmonary disease (COPD), and particularly in individuals with low body weight. Although the mechanisms underlying the development of this condition in COPD patients are poorly understood, the contraction-relaxation cycle in skeletal muscle depends on the cytoplasmic concentration of calcium ($Ca^{2+}$), and proteins of the sarcoplasmic-endoplasmic reticulum $Ca^{2+}$ adenosine triphosphatase (SERCA) family are key regulators of this concentration. Morlà et al[3] investigated abnormalities in the expression and function of SERCA in the skeletal muscle of patients with COPD and low body weight. They found that the expression of SERCA2—a variant of messenger RNA (mRNA) expressed in slow-twitch fibers, cardiac muscle, and smooth muscle (SERCA2a) and also in a number of nonmuscle tissues (SERCA2b)—was lower in the group of patients with COPD and low body weight. SERCA2 was also tyrosine-nitrated in these patients. In an earlier study, the same authors had demonstrated the existence of a negative correlation between SERCA2 levels and concentrations of the inducible isoform of nitric oxide synthase in COPD patients with low body weight.[4] The fact that SERCA2 concentrations are lower and tyrosine-nitrated in the skeletal muscle of these patients is evidence of another cell abnormality that may be clinically significant in that it may limit their exercise capacity and quality of life.

As an alternative to respiratory muscle training with control of breathing pattern, Bustamante Madariaga et al[5] studied an inspiratory muscle training program in which load on an inspiratory muscle training device was adjusted at regular intervals to ensure that it was never too low but breathing pattern was not controlled. In this randomized controlled trial improvement was observed in both peak inspiratory pressures and Chronic Respiratory Questionnaire scores in patients who followed the training program, irrespective of whether a threshold device or a resistive load device was used. The authors did not find one training method to be better than the other.

In a trial that investigated the same subject in somewhat greater depth, Regiane Resqueti et al[6] evaluated the efficacy of a home-based pulmonary rehabilitation program for patients with severe-to-very-severe COPD and incapacitating dyspnea. On the basis of their findings, they confirmed that a pulmonary rehabilitation program including low-intensity muscle training of various muscle groups improved exercise tolerance, dyspnea, and some quality-of-life parameters, and that these benefits were maintained at 6 months in patients following a maintenance program.

The importance of dynamic hyperinflation in triggering dyspnea and limiting exercise tolerance in patients with COPD is well known. Lisboa et al[7] undertook to establish reference values for inspiratory capacity in healthy individuals of both sexes between 50 and 87 years of age in order to remedy the lack of such data in the literature. They found that a model including age, height, and weight produced prediction equations for inspiratory capacity and

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that their results were similar to those obtained by other authors using different models.

To obtain more information concerning the factors predictive of survival in COPD, Solanes et al[8] followed up a group of patients with this disease for 7 years. Overall survival at the end of the study was 53%. Using univariate analysis, they found a correlation between survival and age, degree of obstruction, inspiratory capacity, carbon monoxide diffusing capacity adjusted for alveolar volume, maximum voluntary ventilation, and maximum exercise tolerance. Maximum minute ventilation was the variable that best predicted survival: most of the patients with a maximum minute ventilation over 42 L/min survived the 7-year follow-up compared to under 55% of those with values under this threshold.

The impact of COPD on the daily life of patients is a subject that has been little studied. The aim of the EIME study carried out by Álvarez Gutiérrez et al[9] was to investigate the situation of COPD patients in Spain using a translated version of a disease-specific questionnaire designed to measure the impact of COPD on activities of daily living[10] and to analyze the relationship between the impact scores obtained and clinical parameters, lung function measurements, socioeconomic status, and health-related quality of life (HRQOL) as measured by the St George's Respiratory Questionnaire (SGRQ). They also tried to identify the variables that best defined the profile of the fragile patient requiring special attention. The results of that study confirmed that the ability to carry out the activities of daily living is greatly reduced in patients with COPD. With respect to socioeconomic variables, the profile of the fragile patient was defined by older age, a lower educational level and economic status, and a greater probability of being single, widowed, or living in a nursing or retirement home. The scores obtained on the impact questionnaire correlated closely with HRQOL and with the variables related to disease severity, such as dyspnea, number of exacerbations, and forced expiratory volume in 1 second ($FEV_1$). Moreover, the differences between the fragile and nonfragile patients in these parameters were statistically significant.

To make available more effective and easier-to-use tools for assessing quality of life, Camelier et al[11] evaluated the discriminatory properties and validity of the Airways Questionnaire 20 (AQ20) in a group of patients with obstructive airway disease, and compared its properties with those of the SGRQ and the 36-item Short Form Survey (SF-36). The results obtained with the AQ20 questionnaire correlated closely with the total score on the SGRQ and moderately well with all the SF-36 domains. In the regression model, the elements that best predicted the AQ20 score were baseline dyspnea index and 6-minute walk test distance. When the SGRQ was used as a reference, the level of accuracy achieved by the AQ20 was high.

Dealing with more clinical aspects of COPD, Miravitlles et al[12] undertook a systematic review of the literature and meta-analysis to compare the clinical efficacy of moxifloxacin to that of the other antibiotics routinely used to treat exacerbations of chronic bronchitis. Only 9 of the 45 studies identified fulfilled the inclusion criteria and were included in the meta-analysis. The conclusion was that moxifloxacin was "at least as clinically effective" as the standard treatments to which it was compared. Moreover, analysis of the results of the 9 studies revealed an aggregate mean difference in clinical success rate of 1.5% in favor of moxifloxacin. While not statistically significant, this difference clearly indicates a favorable trend.

Rodríguez Escolar and Fidalgo García[13] investigated trends among primary care physicians in Madrid in the prescription of drugs for the treatment of COPD and asthma during the period 1996-2002 and assessed the impact of new therapies. They found that drug use, expressed as defined daily dose per 1000 population per day, increased by 18.5% between 1996 and 2002, and that the use of inhalants increased by 33% over the same period. The drugs most used were $\beta_2$-adrenergic agonist inhalants (37.7%), anticholinergic agents (22.5%), inhaled corticosteroids (19.5%), combinations of fixed doses of long-acting $\beta_2$-adrenergic agonists with corticosteroids (10.5%) and xanthines (5.0%).

On the subject of treatment with continuous positive airway pressure (CPAP), Neme et al[14] investigated the physiologic effects of noninvasive mechanical ventilation with nasal masks using CPAP and CPAP plus pressure support ventilation. They confirmed that, in patients with severe COPD, CPAP of 3 cm $H_2O$ with pressure support ventilation improved the breathing pattern, increased alveolar ventilation, and reduced work of breathing. These findings provide a rational basis for the use of noninvasive mechanical ventilation in the treatment of these patients.

## Sleep Disordered Breathing

Vidal et al[15] compared the scores obtained by patients with sleep apnea-hypopnea syndrome (SAHS) in the various domains of the Spanish version of the Functional Outcomes of Sleep Questionnaire (FOSQ) with those obtained by healthy controls, and assessed the usefulness of this tool for evaluating the impact of sleepiness on activities of daily living in patients with suspected SAHS. Compared to the healthy controls, the patients with SAHS scored higher on the Epworth sleepiness scale and had a lower mean (SD) score not only on the FOSQ (88.7 [19.8] compared to 110.9 [9.8]; $P<.001$) but also in all its component domains except social outcome (intimacy and sexual relationships, activity level, vigilance, and general productivity). In a logistic regression model, the classification recommended by the American Thoracic Society guidelines was the least predictive of SAHS, while the most predictive variable was the Epworth sleepiness scale. The predictive value of the FOSQ fell between these 2 other alternatives.

In an up-to-date assessment of the diagnosis of SAHS in Spain, Masa Jiménez et al[16] reported on the evolution over time of this situation and provided a useful management tool for both specialists and health care administrations. The main variables used in their descriptive analysis of the diagnosis of SAHS in Spanish hospitals were the length of time patients had to wait for

a consultation or tests and the diagnostic resources available. The mean waiting period was 61 days for a specialist consultation and 224 days for respiratory polygraphy. The mean number of devices available in the country was 0.99 per 100 000 population while the recommended ratio is 3 per 100 000 population. The mean waiting time for polysomnography was 166 days, with a ratio of 0.49 beds for this purpose per 100 000 population, also below the recommended ratio of 1 to 100 000). Clearly, as the authors concluded, resources are currently inadequate, a situation that has given rise to unacceptably long waiting lists.

In a study designed to evaluate simpler diagnostic procedures, Jurado Gámez et al[17] compared the diagnostic validity, degree of patient satisfaction, and cost of home sleep monitoring using polygraphy compared to polysomnography in a sleep laboratory. The results obtained with the 2 methods coincided in 88.4% of the cases studied, with only 1 false positive, which was obtained using polygraphy. The authors concluded that polygraphy was a cost effective and helpful tool for correctly determining the severity of SAHS, with a specificity and sensitivity of 100% in patients with an apnea-hypopnea index higher than 30, and that home polygraphy was associated with higher patient satisfaction than polysomnography in a sleep laboratory. A similar study of adults with suspected SAHS carried out in Mexico City revealed a high level of agreement between the desaturation index and both the apnea-hypopnea index obtained by polysomnography and the respiratory disturbance index.[18] The authors of that study also confirmed that altitude did not affect the diagnostic yield of the portable device used to measure oxygen saturation.

In addition to the difficulties associated with the diagnosis of SAHS, ensuring compliance with prescribed therapy is also a problem in these patients. Torre Bouscoulet et al[19] investigated what proportion of patients diagnosed with SAHS in Mexico City were adhering to an adequate treatment regimen. The main variables studied were whether patients acquired a CPAP device and whether they subsequently complied with the prescribed treatment regimen. The authors of that study found that the patients who acquired the device had a higher respiratory events index and a lower mean oxygen saturation during sleep than those who did not. The respiratory events index was also the only factor significantly associated with treatment compliance. A noteworthy finding was that almost half of the patients without public health insurance coverage who were prescribed CPAP never started treatment.

Another aspect of interest in SAHS is the diagnosis and treatment of the syndrome in specific groups or under different circumstances. Llombart et al[20] found no differences in clinical characteristics or sleep patterns between a group of children with SAHS and tonsillar hypertrophy and a group with SAHS and other diseases or disorders (Down syndrome, Prader-Willi syndrome, cystic fibrosis, ciliary dyskinesia, morbid obesity, Pierre Robin syndrome, Rett syndrome, and neuromuscular disease), although the clinical course was more favorable for the children with tonsillar hypertrophy.

## Lung Function

Electrical impedance tomography, a noninvasive technique used to obtain chest images during spontaneous breathing, has been shown to be effective in assessing lung function. Balleza et al[21] compared this imaging technique to pneumotachography for monitoring resting breathing pattern, demonstrating that similar tidal volume measurements were obtained with both techniques. The implication of their findings is that electrical impedance tomography represents a significant advance because it will, in the not-so-distant future, provide a reliable, simple, reproducible, noninvasive, and economical way to monitor breathing pattern.

Since a number of international consensus statements recommend the assessment of certain respiratory diseases after the administration of a bronchodilator, the aim of a study by Pérez Padilla et al[22] was to determine postbronchodilator spirometry reference values. The most interesting finding in that study was that postbronchodilator reference values for $FEV_1$, ratio of $FEV_1$ to forced vital capacity, and ratio of $FEV_1$ to $FEV_6$ were on average 3% higher than the results of baseline spirometry. This difference caused an upward shift in the 5th percentile (lower limit of normal) of the predicted values. When prebronchodilator rather than postbronchodilator reference values were used, 3.2% of the reports of airflow limitation were false negatives in this population of patients over 40 years of age.

## Asthma

Urrutia et al[23] studied changes in the prevalence of asthma after a period of 9 to 10 years in a cohort of young adults who participated in the Spanish arm of the European Community Respiratory Health Survey (ECRHS). They found that the prevalence of wheezing in the preceding 12 months had increased from 10% to 33% among new smokers, and that the prevalence of sputum production rose from 8% to 22% in the same group. By contrast, in the group of patients who had stopped smoking, prevalences of wheezing and expectoration declined from 21% to 12% and 15% to 8%, respectively. No differences were found in symptoms in the patients who had never smoked, but an increase was observed in the prevalence of diagnosed asthma.

In another study, Morell et al[24] demonstrated that patients with asthma had fewer exacerbations and that the use of health care services, both scheduled and emergency, improved when the treatment prescribed by primary care physicians followed the recommendations of international guidelines and was accompanied by a brief explanation of the disease.

Báez Saldaña et al[25] published a self-administered questionnaire in Spanish designed to assess how much asthma patients know about their disease. The resulting questionnaire has face and content validity, is appropriately structured, fulfills criteria for consistency and precision, and has been shown to be reliable and sensitive to the changes that occur after an educational intervention.

Pérez Yarza et al[26] undertook a prospective national multicenter observational study of 387 asthmatic children to determine whether variability in peak expiratory flow could be used to classify the level of severity of childhood asthma. The participants had all been diagnosed with asthma and were aged between 6 and 14 years. While no correlation was observed between clinical classification of severity and the variability of peak expiratory flow, monitoring this variable may be useful when the diagnosis is uncertain, for identifying asthma triggers, and in difficult-to-control asthma or cases in which bronchial obstruction is not perceived but the patient experiences frequent severe attacks. In another study of childhood asthma, Mir Messa et al[27] assessed the safety of tracheal auscultation for measuring bronchial hyperresponsiveness to methacholine in healthy children under 4 years of age, and found it to be a simple, appropriate, and safe method.

## Smoking

Nerín et al[28] evaluated the results of smoking cessation therapy in a specialist unit by calculating the probability of sustained abstinence on follow-up at 6-months and by analyzing differences on the basis of individual characteristics. Survival analysis, used to assess the likelihood of the patients remaining abstinent, revealed that the probability of a subject continuing to refrain from smoking ranged from 86.3% at 1 week to 62.2% at 6 months; no gender-related differences were observed. The patients with the most severe dependence were less likely to remain abstinent, and good treatment adherence was a significant determinant of success.

In another interesting article, Barrueco Ferrero et al[29] reported the results of a study to investigate the situation on follow-up at 5 years of smokers who had quit smoking with the help of a tobacco cessation program. Based on their findings, the authors raised 2 important points: the need to identify which patients stop smoking within 2 months because almost half of this subgroup will remain abstinent and will never resume the habit; and the importance of extending the length of the follow-up period after tobacco cessation programs to more than 1 year.

One of the concerns most often raised by smokers who wish to give up the habit is the weight they may gain during the process of quitting.[30] Nerín et al[31] showed that weight gain among individuals who stop smoking after a tobacco cessation program is moderate and found no relationship between weight gain and the anxiety associated with cessation. They also commented that the patients with the lowest weight gain overall were the group who reported smoking their first cigarette more than 60 minutes after waking up in the morning. When the same analysis was done by gender, the difference was maintained for women but not for men.

The negative impact of tobacco use on the smoker's quality of life is well known. Investigating this phenomenon in 3 health care facilities in Seville province, Cayuela et al[32] analyzed the association between tobacco use and HRQOL in male smokers and nonsmokers with no history of chronic disease. They found that, in effect, even male smokers who have not developed any smoking-related comorbidity have a poorer HRQOL than nonsmokers.

When González Barcala et al[33] assessed the repercussions of passive smoking on the lung function of children and adolescents, they found that overall mean spirometric values were significantly lower among the children with a parent who smoked, and that the negative effect of passive smoking on the parameters related to the distal airway was greater. The fact that both parents smoked did not further increase the risk of reduced lung function.

In a bibliometric study of the literature related to smoking, Granda-Orive et al[34] used the Science Citation Index (SCI) database to analyze Spanish research activity on the subject of tobacco use during the 5-year period from 1999 to 2003, and to situate the Spanish contribution within the context of the European Union and the world. One of the most significant findings in this study was that, according to the SCI data, the subspecialty areas with the largest output related to smoking were public health, health education and economics, respiratory and internal medicine, and experimental research. The articles were published in a broad range of journals, and Madrid and Barcelona were the provinces with the highest output. The number of articles published in collaboration is an indicator of the international projection of Spanish research because 29.5% of all articles were written with international co-authors. Furthermore, the first author was a foreigner in 15.4% of the manuscripts. The factors associated with a higher citation rate were publication in English, international collaboration, and having a non-Spanish first author.

Analysis of the structure of scientific collaboration networks is also of great interest. In a study of scientific collaboration, Villanueva Serrano et al[35] found that 35 Spanish medical centers located in 8 autonomous communities had participated in 21 research projects involving interinstitutional collaboration on a national level during the period studied.

## Oncology

To assess the risk factors associated with lung cancer surgery, Duque et al[36] analyzed the incidence of postoperative complications and mortality in these patients. Multivariate analysis of the data confirmed the impact of major complications on mortality, with cardiovascular complications being associated with the highest risk. The overall mortality rate in that study was 6.8%, and the groups with the highest mortality were the patients who developed major complications and those who underwent pneumectomy. On the basis of these findings, the authors concluded that surgical treatment of lung cancer is associated with high morbidity and mortality in Spain.

Surgical resection, the treatment of choice in the early stages of bronchogenic carcinoma, is ruled out if the patient is expected to have a postoperative $FEV_1$ of less than 800 mL. Gómez Sebastián et al[37] made the point that comorbid COPD—the disease that most often accompanies lung cancer in Spain—often makes it difficult for these patients to fulfill this criterion for operability. They went on to hypothesize that it might be possible for certain patients previously classified as inoperable to

achieve the necessary threshold level with an intensive preoperative program (which they called a "rescue" program) involving tobacco cessation, optimization of pharmacological treatment, and pulmonary rehabilitation. After following this program, 24 patients (80%) showed a clinically and statistically significant improvement in all the lung function parameters analyzed. The improvement was sufficient to ensure that all of them met the criteria for postoperative lung function and they were therefore given the option of undergoing surgery. Based on their results, the authors concluded that a rescue program of this type makes it possible to propose surgical treatment to a large number of patients with lung cancer in whom surgery has previously been ruled out.

With respect to other therapeutic options for lung cancer patients, it has been shown that the treatment of stage III non-small cell lung cancer using a combination of chemotherapy and radiation therapy administered concurrently is associated with longer survival. However, because of the higher toxicity and practical difficulties associated with such regimens, physicians must be more selective and have a clear understanding of the criteria for treating these patients with such concurrent therapy. The objective of a study by Sánchez de Cos Escuín et al[38] was to analyze survival and adverse effects in patients with stage III non-small cell lung cancer following a sequential combined-modality regimen of chemotherapy and radiation therapy. The secondary aim was to identify the variables that could improve patient selection for such regimens. They reported a median survival time of 14 months and a 3-year survival rate of 16.1%. The variables predictive of shorter survival in the multivariate analysis were poor general condition (grade 2 on the Eastern Cooperative Oncological Group performance scale), anemia, and elevated serum concentrations of carcinoembryonic antigen. Univariate analysis revealed that weight loss and diagnosis before the year 2000 were also associated with poorer prognosis. Patients with stage IIIa tumors (TNM system) tended to have a better prognosis than those with stage IIIb disease, but the difference was not significant. Another interesting finding in this study was that a favorable objective response (partial or complete remission) was associated with longer survival.

Estrada Trigueros et al[39] studied the general clinical characteristics and overall survival at 5 years of all of the patients diagnosed with bronchogenic carcinoma in their hospital in 2000 and 2001. The overall survival rate for bronchogenic carcinoma of any histological type was 13.3% (median survival, 10 months). When the study population was divided into 2 groups according to age (median, 68 years), it was found that 5-year survival was significantly worse in the older group. None of the patients with small cell tumors survived for 5 years (although those with disease confined to the chest had a better 3-year survival rate than those with extrathoracic extension). By contrast, the 5-year survival rate among the patients with non-small cell tumors was 15.4%. They also analyzed 5-year survival by clinical stage and, logically, found a longer survival time among patients diagnosed in the lower stages. Based on these findings, the authors concluded that the epidemiological profile of the population studied was similar to that described in other studies carried out in Spain. Bronchogenic carcinoma is still diagnosed in advanced stages and only a small number of patients are treated with intention to cure.

The objective of a study published by Paredes Lario et al[40] was to evaluate the influence of the expression of membrane transporter proteins on chemotherapeutic response. Using immunohistochemical analysis, they measured the expression of Pgp, MRP1, and LRP (proteins associated with multidrug resistance) in tumor samples collected from patients with lung cancer and analyzed the relationship between such expression and the patients' response to chemotherapy. No correlation was found between the expression of any of the 3 proteins studied and any prognostic factors, such as staging, and neither did the expression of these proteins appear to affect either survival or risk of recurrence. These results indicate that resistance to chemotherapy is multifactorial, making it unlikely that any single mechanism of resistance will offer the key to overcoming the phenomenon as a whole.

Another important issue related to lung cancer is the yield of the available diagnostic tests. Consequently, Sánchez de Cos Escuín et al[41] undertook a study to evaluate the yield of cranial computed tomography (CT) and magnetic resonance in the detection of silent brain metastasis during the initial staging of patients with lung cancer. They detected silent brain metastasis in 8.3% of patients who presented no neurological symptoms at the time of diagnosis. The detection rate was 7.9% in the CT group and 11.3% in the magnetic resonance group. There were no false positive results, and the overall false negative rate was 1.9%. More cases of multiple metastasis were identified by magnetic resonance imaging than by CT. They also reported that the incidence of metastasis was lower in the group of patients aged 70 years and over and higher among the patients with adenocarcinomas.

García Yuste et al[42] studied trends in a series of prognostic factors in patients with neuroendocrine lung tumors by analyzing data from their own earlier study[43] and subsequently recorded cases. The authors established 2 groups: the first comprised the cases included in the earlier study and the second included those who enrolled in the second phase between 1998 and 2002. All of the tumor samples were reviewed and classified according to the new World Health Organization classification, including the new criteria developed by Travis for classifying atypical tumors.[44] After analyzing the results of surgical treatment, the authors concluded that a discernible trend was apparent in the prognostic factors related to neuroendocrine lung tumors. They also suggested that a better understanding of both treatment and prognosis could be achieved through the application of general criteria in the staging and choice of a treatment strategy in these patients.

Muñoz Llerena et al[45] studied the prognostic factors associated with survival in a series of patients who underwent resection of pulmonary metastases from colorectal cancer in a single hospital over a 10-year period.

All of the patients were treated on the basis of consistent surgical and oncological criteria. Those authors reported that the size of the largest metastasis and the level of carcinoembryonic antigen were the preoperative variables that best predicted survival. They also made the point that surgery should be considered in all patients with potentially resectable lung metastasis from colorectal cancer in view of the lack of any universally accepted predictors.

If correct diagnosis and staging are critical in lung cancer, the repercussions of delaying surgery are no less important in the survival of these patients. In a study designed to assess the effects of delaying surgery, Cañizares Carretero et al[46] found no significant differences in the time elapsed before surgery in relation to tumor stage, type of surgery, patient age, or complete resection rate. Nor did they find any evidence that delays in performing surgery affected survival. Tumor stage, complete resection of the tumor, and patient age were the most important prognostic factors.

## Tuberculosis and Cystic Fibrosis

### *Tuberculosis*

It is thought that larger tuberculin reactions occur more often in patients with active tuberculosis and in infected patients at greater risk for developing active disease. Alseda and Godoy[47] studied the size of tuberculin reactions in contacts with positive tuberculin skin test results and analyzed the association between induration size and the following variables: contact age, the variables relating to risk of disease transmission (the degree of contact with the index case and the index patient's sputum smear result), and the presence of active disease in the contact. Their results demonstrated that contact investigations should be prioritized according to probable yield and confirmed that, among contact with positive tuberculin skin test results, larger reactions were associated with recent infection in the contacts (entailing greater risk of developing active disease), greater exposure to contagion (close contact with a smear-positive index patient), and the diagnosis of active tuberculosis in the contact in the course of investigation.

In another similar study, Salinas et al[48] confirmed that the contact investigation is still an effective strategy for finding new cases of tuberculosis, facilitating early diagnosis, and thereby preventing further disease progression. They stress that prophylactic treatment should be started as soon as possible, giving priority to the contacts of smear-positive index cases and patients under 45 years of age. They also indicated that a threshold of 10 mm for the diameter of the tuberculin skin reaction has greater discriminatory power than diameters under 5 mm, and that routine chest radiography may not be necessary in contacts with indurations under 10 mm given the high sensitivity of this threshold.

All the autonomous communities in Spain have implemented tuberculosis control programs to identify infected individuals and have opened clinics specifically for this purpose. Galicia is a case in point. In an investigation of tuberculosis microepidemics, Marcos Rodríguez et al [49] concluded that contact tracing based on a concentric circle strategy predicts risk of infection with great precision, and that the strains isolated from the patients should be investigated using restriction fragment length polymorphism analysis to identify transmission pathways.

The increase in the prevalence of resistant *Mycobacterium tuberculosis* strains is currently a cause for serious concern. For this reason, Sanz Barbero and Blasco Hernández[50] analyzed the resistance patterns in strains of *M tuberculosis* isolated in the foreign-born population resident in the Autonomous Community of Madrid, and determined the variables associated with such resistance. Their analysis revealed an overall resistance rate of 14%. Analysis by drug produced the following results: 10.9% of strains were resistant to isoniazid, 5.4% to streptomycin, 4.5% to rifampicin, 2.3% to pyrazinamide, 23% to rifabutin, 0.9% to ethambutol, and 0.5% to ethionamide, ofloxacin, paraaminosalicylic acid, and thiacetazone. The rate of single-drug resistance was found to be 7.6%. Resistant strains were isolated in 12.6% of the new cases and in 27.3% of the cases of patients who had previously received antituberculosis treatment. Overall, 4.5% of the strains isolated were found to be multidrug resistant, and such resistance was associated with a history of prior antituberculosis treatment. The most important conclusions of that study were that antituberculosis treatment should be initiated with a combination of 4 drugs until the results of sensitivity tests are available and that a prior history of antituberculosis treatment should raise the suspicion of multidrug resistance.

### *Cystic Fibrosis*

It is of great interest to have information on the energy requirements of a patient with cystic fibrosis when drawing up a personalized nutrition plan. Indirect calorimetry is the ideal technique for determining basal energy expenditure. However, because of the complexity of this technique, a number of different equations have been developed to predict basal or resting energy expenditure in these patients. Individual physical activity and disease severity are accounted for by the application of correction factors. Olveira Fuster et al,[51] in a study of adults and adolescents with cystic fibrosis, compared basal energy expenditure determined by indirect calorimetry with the value obtained using these predictive equations, and also assessed the influence of a series of clinical variables. They found that the equations normally used to calculate this expenditure in adults with this disease systematically underestimated the actual expenditure, irrespective of the value. The difference between the actual expenditure determined by calorimetry and the value predicted was greater in patients with more severe disease.

Advances in the care of patients with CF have greatly increased the life expectancy of these patients. However, besides increasing the "quantity" of life, it is also important to improve "quality" of life in this setting. Assessment of HRQOL in patients with cystic fibrosis provides additional

information on the impact of the disease that cannot be obtained by means of other purely physical assessments, such as lung function tests or nutritional status. Padilla et al[52] assessed HRQOL in adults with this disease, using the SGRQ, also evaluating the validity and consistency of this tool. They concluded that the questionnaire was valid for analyzing HRQOL in adults with CF because it discriminates well between the different degrees of severity of lung function impairment and has acceptable internal consistency.

## Circulation

Cardiac, respiratory, and systemic diseases can be diagnosed and monitored by measuring pulmonary artery pressure. To validate a noninvasive indirect method based on the measurement of jugular blood flow using transcutaneous Doppler ultrasound, Blanco Vich et al[53] investigated the estimation of pulmonary artery pressure through analysis of the flow velocity waves in the right brachiocephalic vein. On the basis of their findings, the authors recommended transcutaneous Doppler ultrasound for the estimation of pulmonary artery pressure in patients with respiratory diseases. This is a simple, noninvasive procedure that can even be performed in the office of the respiratory medicine specialist during a consultation.

The objective of a prospective study by Jiménez et al[54] was to determine the prognostic value of transthoracic echocardiography in a consecutive series of hemodynamically stable patients with acute symptomatic pulmonary embolism. The authors did not find the technique to be useful for risk stratification of hemodynamically stable patients, and therefore recommended that appropriately designed prospective studies should be carried out to determine where this method might be useful.

In a more practical vein, Uresandi et al[55] undertook a multicenter study to develop a prediction rule for identifying short-term risk of adverse events in patients with pulmonary embolism. The scale they developed adequately predicted whether a patient was likely to develop complications during the first 10 days following an acute episode of pulmonary embolism. Assessment of diagnostic efficacy for a cutoff of 2 points gave an area under the receiver operating characteristic curve of 0.75. Thus a patient with a score of 2 points or less would be at low risk for developing complications from pulmonary embolism in the short term

Otero González et al[56] described the clinical and functional characteristics of patients with pulmonary artery hypertension and chronic thromboembolic pulmonary hypertension in functional classes II and III and studied the response of these patients to treatment with sildenafil as monotherapy. The authors concluded that, despite the small number of patients in the study, their results supported the use of sildenafil as an effective drug for the management of pulmonary artery hypertension and chronic thromboembolic pulmonary hypertension in both the short and long term, with a good level of tolerance and few side effects.

## Diagnostic Techniques and Lung Transplantation

### *Diagnostic Techniques*

Ferández Villar et al[57] studied the individual and combined yield of transbronchial biopsy and transbronchial needle aspiration and evaluated the clinical usefulness of both techniques in the diagnosis of sarcoidosis in stages I and II. In cases with parenchymal involvement, the combined use of both techniques had a significantly higher diagnostic yield than either technique used separately, while in cases in which no such involvement was observed, the combination had a significantly higher yield than transbronchial biopsy alone. Analysis of bronchoalveolar lavage revealed a $CD4^+/CD8^+$ ratio greater than 3.5 in 42.8% of patients. Bronchial biopsies were performed in 10 patients and were positive in 50% of these cases. The authors concluded that the use of transbronchial needle aspiration to complement transbronchial biopsy significantly increases the number of diagnoses of sarcoidosis obtained, particularly in patients without parenchymal involvement. They reported few complications and good tolerance.

Endoscopic ultrasound (EUS) is an imaging technique that combines gastrointestinal endoscopy and ultrasound to obtain images from within the digestive tract. Fernández Esparrach et al[58] assessed the usefulness of EUS-guided fine needle aspiration for cytologic diagnosis of mediastinal lesions in a Spanish tertiary level hospital. They concluded that EUS-guided fine needle aspiration was a safe and effective technique for assessing mediastinal lesions, that it could evaluate affected lymph nodes too small to be characterized by CT, and that the probability of malignancy was greater the larger the size of the lesion. A noteworthy finding was that of some 37 enlarged lymph nodes with a short axis diameter of less than 1 cm, 5 (5.6%) were malignant. This is important because the diagnosis of metastatic nodes by CT depends on size, while the usefulness of EUS-guided fine needle aspiration in the staging of non-small cell lung cancer is well known.

### *Lung Transplantation*

Navas de Solís et al[59] designed a retrospective cross-sectional study of 54 patients with cystic fibrosis to ascertain whether the incidence of diabetes in these patients increases following lung transplantation. They concluded that lung transplantation was the most important risk factor for developing diabetes in these patients. Despite the significant limitation, recognized by the authors, of the small number of patients studied, their findings serve to highlight the importance of careful long-term monitoring of blood sugar levels in cystic fibrosis patients following lung transplantation even among those with previously normal glucose tolerance.

In view of the lack of agreement between the authors who have studied donor lung ischemic time and its relation to complications such as ischemia-reperfusion injury and acute organ rejection, Santana Rodríguez et al[60] undertook an experimental study to clarify the possible role of ischemic time in the development of these complications.

They concluded that a longer ischemic time was not associated with more severe ischemia-reperfusion injury, acute organ rejection, or a poorer clinical course, and that rejection was unrelated to either the presence or severity of a parenchymal injury.

The restoration of blood flow after ischemia further aggravates tissue damage that started during the ischemic period and the process mimics some of the characteristics of acute inflammatory reaction. Leukocyte chemoattractants, and in particular chemokines, appear in tissues and play a key role in the pathogenesis of ischemia-reperfusion syndrome and nonspecific graft dysfunction. These include interleukin 8, which is the principal member of a large family of chemotactic cytokines and which initiates highly selective recruitment of polymorphonuclear cells into tissue from peripheral blood. Matilla et al[61] analyzed the expression of interleukin 8 mRNA in lung tissue and the association between these levels and interstitial lung changes in an experimental model of warm lung ischemia-reperfusion. They observed that changes in interleukin 8 mRNA during ischemia preceded interstitial infiltration by polymorphonuclear cells during reperfusion—a finding indicating a relationship between the 2 processes. Their conclusion was that quantification of such mRNA could be useful in the diagnosis and monitoring of early graft dysfunction.

## Management

Campos Rodríguez et al[62] found a low rate of inappropriate stays after admission by a pulmonology department and observed that the patients involved were generally waiting for diagnostic tests or results. The variables that best predicted inappropriate stay were diagnosis on admission, the season of the year, and admission to a ward other than the pulmonology ward.

## Pleura

Haro Estarriol et al[63] studied a group of patients with lymphocytic exudate of varying etiologies to assess the changes that occurred in the cytologic and biochemical parameters of pleural fluid following thoracentesis and transthoracic needle biopsy of the pleura. They determined the clinical significance of any such changes paying special attention to the etiology of the effusion, the levels of any inflammatory markers such as lactate dehydrogenase, and the presence of eosinophils in pleural fluid. Serial measurement of the influence of thoracentesis and pleural needle biopsy revealed no significant changes in the cytology and biochemistry of pleural fluid and showed that lactate dehydrogenase levels increased after biopsy in patients with pleural tumors or baseline concentration greater than 266 U/L.

In an interesting study, Martínez Ramos et al[64] could not demonstrate that the presence of bullae was associated with increased risk of recurrence following a first episode of spontaneous pneumothorax. They concluded that although the bullae have little influence on recurrence, there is a tendency for the patients who have them to experience recurrence earlier, although it was impossible to rule out an effect of chance. Based on the evidence, therefore, the authors could not recommend surgery for the prevention of recurrence in these patients.

## Miscellaneous Factors

Rivo Vázquez et al[65] analyzed the impact of the learning curve on the preliminary results of video-assisted thoracic surgery for spinal deformities performed in a general hospital setting, concluding that that this technique will inevitably be incorporated into standard practice in the near future, despite its technical complexity. They reported that the steep learning curve is manageable in a general hospital if these procedures are carried out jointly by thoracic and orthopedic surgeons.

Güell et al,[66] who investigated the management of patients with Duchenne muscular dystrophy, concluded that respiratory support confers clinically significant benefits and should be offered to all patients with a view to prolonging survival. Careful monitoring of clinical and functional parameters is necessary to prevent respiratory failure and the need for tracheostomy.

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