

Short report, EXP-O 2008

Expert Opinion Consensus/Dissensus Seminar - "COPD is/is not a systemic disease?", Venice, Italy, November 13-14, 2008

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## EXP-O 2008, Expert Opinion Consensus/Dissensus Seminar "COPD is/is not a systemic disease?", Venice, November 13-14, 2008: short report

EXP-O 2008, Seminario di consenso/dissenso - l'opinione degli esperti su: "La BPCO è/non è una malattia sistemica?", Venezia, 13-14 novembre, 2008: breve resoconto

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### INTRODUCTION

In recent years, some authors maintain that chronic obstructive pulmonary disease (COPD) and its comorbidities should come under a new umbrella term - chronic systemic inflammatory syndrome - because the systemic effects of smoking contribute to several other conditions, including cardiovascular disease, cancer, and increased blood pressure. Such a view would open up vast new horizons for internal medicine.

Unfortunately this view is poorly supported by the scientific literature and should be regarded more as a fascinating speculation than as an evidence based proposition. It overlooks the possibility that all the so-called comorbidities described in association to COPD - e.g. skeletal muscle abnormalities, hypertension, diabetes, coronary-artery disease, heart failure, pulmonary infections, cancer, and pulmonary vascular disease - could simply be independent diseases frequently found in subjects with

the age, risk factors and lifestyle of COPD patients. This latter objection may seem "old hat" but it is perhaps more realistic than espousing a point of view which, though novel and appealing, at present has little to do with evidence-based science.

With the aim of clarifying this debate in a rigorous scientific context, the Italian Interdisciplinary Society for Research in Lung Disease (AIMAR) organized, as part of its "AIMAR Top Seminars 2008" program, a dedicated scientific event in Venice on November 13-14, 2008: EXP-O 2008 - Expert Opinion Consensus/Dissensus Seminar - "COPD is/is not a systemic disease?". The aim was to bring together the sustainers of both sides in a format that allows the best opportunity for discussion and debate (two 15-minute interventions "pro" and "con" on each subject followed by a 30-minute discussion amongst a highly select faculty audience, then, in the afternoon, a further session aimed to achieve a consensus or dissensus on the conclusions that emerged in the morning). Leading authors and

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about 40 highly qualified discussants with major expertise in the field participated. The object was to arrive at a final consensus or dissensus on this topic, and produce a Statement to clarify the issue for practising clinicians.

**Pathophysiological basis of COPD: the Pro systemic side (Paolo Palange, Rome, Italy)**

COPD has traditionally been considered a disease of the lungs secondary to cigarette smoking and characterized by airflow obstruction due to abnormalities of both airway (bronchitis) and lung parenchyma (emphysema). It is well known that COPD is associated with significant systemic abnormalities: in the late '80s it was documented that chronic hypoxia and hypercapnia can induce renal and hormonal abnormalities in COPD patients with chronic bronchitis (type-B) [1]. More recent evidence shows that a significant proportion of patients with COPD, particularly those with predominant emphysema (type-A), may experience muscle wasting [2], osteoporosis [3], anemia [4] and reduction in circulating bone marrow progenitors [5]. These systemic abnormalities have been attributed to increased levels of systemic inflammation, e.g. increased levels of tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-6. Some have hypothesized that systemic inflammation is due to a "spilling over" of the pulmonary inflammation into the systemic circulation [6]. Others, who failed to demonstrate a correlation between lung and systemic inflammation [7], raised the question if COPD may not be in fact a systemic disease. Chronic inflammation, however, may not be the only cause of the systemic effects of COPD. Recent data, in humans and animal models, show increased levels of endothelial cell apoptosis and reduced levels of angiogenic factors, e.g. vascular endothelial growth factor (VEGF) in the lung in response to cigarette smoking and oxidative stress, suggesting that emphysema may be a vascular disease [8]. Other studies claim that pulmonary emphysema carries an autoimmune component [9]. Based on this new evidence, it is reasonable to consider COPD, in particular emphysema, as a disease with a significant "systemic component" if not a systemic disease *per se*.

**Pathophysiological basis of COPD: the Non systemic side (Andrea Rossi, Bergamo, Italy)**

COPD is one of the few respiratory disorders that includes in its definition a reference to lung function [10]. The pathophysiology of COPD includes a wide array of abnormalities [11] in lung and chest wall mechanics, pulmonary gas exchanges, respiratory and skeletal muscle structure and function, and so on [12]. COPD is a heterogeneous disease in terms of its clinical, physiological and pathological presentation [13]. Probably the starting point is inflammation of the airways [14,15] and the final events are severe physical disability and premature death. Within this complexity, airflow limitation is a central element, and to some extent the bridge, connecting biological defects to clinical pheno-

types. Without doubt, airflow limitation is a key mechanism determining dyspnea, progressive disability, and ventilatory failure in patients with COPD [16]. Understanding the pathophysiology of airflow limitation is an essential step to alleviating suffering, through effective interventions such as pharmacological therapy, rehabilitation, lifestyle changes, and so on [10,17-19]. The literature on airflow limitation in COPD is abundant [20-23]. It is important to stress the distinction between airway obstruction and airflow limitation and the close relationship between the latter and pulmonary hyperinflation: airway/airflow obstruction and airflow limitation should not be considered, either academically or in clinical practice, as synonymous.

**COPD and systemic inflammation: myth or reality? Pro Reality (William MacNee, Edinburgh, UK)**

COPD is an inflammatory condition of the lungs which has recently been recognized as a systemic disorder with important extrapulmonary manifestations [24]. It is thought that systemic inflammation is the mechanism which results in these systemic manifestations. A systemic inflammatory response is known to occur in COPD and involves mobilization and activation of inflammatory cells into the circulation and an increase in acute phase proteins and in circulating inflammatory mediators. C-reactive protein (CRP) is a robust marker of the acute phase response. It has been shown in large cohort studies that subjects with severe airflow limitation are 2.74 times more likely to have an elevated CRP [25], independently of cigarette smoking and other associated comorbidities which may influence CRP, such as the presence of coronary artery disease [26]. Increased circulating levels of CRP in COPD are associated with increased IL-6 levels, which is the predominant cytokine regulating CRP production by hepatocytes. Also other acute phase proteins such as fibrinogen are elevated in COPD subjects, particularly those with symptoms of chronic bronchitis [28]. These data suggest that CRP may be a useful biomarker for COPD severity, the systemic inflammatory response associated with COPD and the consequent systemic comorbidities/complications. A number of studies have shown higher levels of circulating inflammatory mediators in COPD patients [27-29]. Increased levels of TNF- $\alpha$  and its receptors TNFR-55 and TNFR-75 have been associated with activation of circulating leukocytes [30] and weight loss in patients with COPD [31]. COPD is associated with low grade systemic inflammation [6,32-34] and circulating leukocytes are present in increased numbers in COPD patients and have been shown to be activated [30,35]. Similar low grade inflammation occurs in other chronic conditions such as chronic heart failure, obesity or diabetes and as part of the normal ageing process [36,37]. Thus, compared with healthy controls, individuals with chronic airflow limitation have significantly elevated levels of CRP, fibrinogen, leukocytes and TNF- $\alpha$ , indicating that persistent systemic inflammation is present in

COPD. This effect is persistent among current non-smokers with COPD. However a mechanism of the systemic inflammatory response in COPD is still unknown and may relate to spill over from the lungs to the systemic circulation or there may be common genetic or constitutional factors which predispose individuals to COPD or to either systemic or pulmonary inflammation. Other potential origins of systemic inflammation in COPD include cigarette smoking, lung hyperinflation, tissue hypoxia, skeletal muscle dysfunction and a response of the bone marrow [38]. It is likely that systemic inflammation is a major contributor to the pathobiology of the extrapulmonary effects of COPD including skeletal muscle atrophy and dysfunction and cardiovascular disease.

#### **COPD and systemic inflammation: myth or reality? Pro Myth (Giuseppe Di Maria, Catania, Italy)**

COPD clinical presentation is characterized by a variety of phenotypes [39]. The variable coexistence of other morbidities including chronic heart failure and elevated blood pressure has long been recognized in patients with chronic bronchitis and emphysema [40]. Thus the complexity and the variability of COPD, along with its frequent association with other morbid conditions, are longstanding concepts for those familiar with COPD patients in their clinical setting. More recently, it has been pointed out that COPD and its inflammatory process affects other end organs [41,42], and the notion that COPD is a "systemic inflammatory disease" has received much attention [43,44]. This notion is based on the observation that COPD and other clinical manifestations are associated to the presence and/or increase of inflammatory biomarkers in the blood. However, the term "systemic inflammation" which, until recently, has been used to indicate the detectable presence of such biomarkers, is misleading in that, according to current evidence, it merely reflects the presence and level of inflammation in the lungs [45,46]. In addition, the role of inflammation in the peripheral muscle wasting and weakness of COPD has never been directly demonstrated by experimental studies. Thus it is true to say that circumstantial evidence, rather than experimental data, support the speculation that COPD is part of a systemic inflammatory process. On the other hand it should be borne in mind that the lungs, by providing efficient gas exchange at the alveolar-to-capillary interface, play a pivotal role in achieving and maintaining the whole body (i.e. systemic) homeostasis. In turn, this homeostasis is of fundamental importance for all the physiological processes of cells, tissues and organs that constitute the body system [47]. Thus it is not surprising that the persistent functional impairment of the respiratory processes may have a negative repercussion on respiratory and metabolic functions of cells and tissue in the body without this necessarily implicating systemic inflammation. COPD may have systemic detrimental consequences involving a number of organs and tissues in the body (i.e. skeletal muscles,

bones and cardiovascular system). The causes of these consequences are complex and poorly understood, but they have been unduly attributed to a putative "systemic inflammation" along with the oxidative damage suffered by COPD patients. Mankind has an innate need to create myths and believe in them. But opinions based on circumstantial evidence are not a sure way to arrive at the truth.

#### **Biomarkers of systemic involvement in stable COPD: do they exist? – Yes (Emiel F.M. Wouters, Maastricht, The Netherlands)**

Biomarkers are factors that are objectively measured and evaluated as indicators of normal biologic processes or pathogenic processes and/or as indicators of pharmacologic responses to therapeutic intervention. Clinical end points are variables that can be used to measure how patients feel, function, or survive. Surrogate end points are biomarkers that are intended to substitute for a clinical end point. Several biomarkers may be needed to create an ideal surrogate end point cluster to truly characterize clinical end points. Individual biochemical or molecular markers can be used as biomarkers to evaluate disease progression and to evaluate the effects of therapeutic intervention early in development. Biomarkers need to represent mechanism-based processes and can provide exciting clues to the pathophysiology of diseases. Therefore, the ideal biomarker increases pathologically in the presence of the disease (high sensitivity), does not increase in the absence of disease (high specificity), offers information about the risk and prognosis, changes in accordance with the clinical evolution, creates opportunities to anticipate clinical changes, relates to disease burden and extent, needs to be reproducible, and optimally will be cheap and easy to measure. The need for biomarkers in COPD research to better diagnose and to assess phenotype, severity, and the effects of treatment is well recognized. COPD is both a pulmonary and a systemic disease. The systemic complications of COPD include nutritional abnormal body composition, muscle wasting, and exercise limitation, as well as involvement of other organ systems (cardiovascular, neurologic, and skeletal).

Most of these complications are, at least in part, thought to be the consequence of systemic inflammation, and accordingly most of the systemic biomarkers are related to inflammatory processes [34]. A meta-analysis conducted in 2004 by Gan and colleagues [34] selected 14 studies that evaluated systemic inflammatory markers in patients with COPD. Levels of CRP, fibrinogen, TNF- $\alpha$  and circulating leukocytes were higher in patients with COPD compared to controls. Several studies have confirmed this COPD-related elevation in CRP. CRP levels have also been shown to relate to COPD severity, both in terms of lung function and St George's Respiratory Questionnaire (SGRQ) score, as well as mortality and disease progression. Pinto-Plata [48] used a proteomics approach to identify a

panel of 24 specific biomarkers in the blood of patients with COPD and demonstrated significant correlations of these biomarkers with forced expiratory volume at 1 second (FEV<sub>1</sub>), diffusing capacity, 6-minute walking distance, and the BODE index. Patients with COPD who lose weight, particularly fat-free mass, represent a COPD phenotype that is in part the result of systemic inflammation. A similar result was obtained by Di Francia and colleagues [30] when patients were divided into groups according to whether or not they had intentionally lost weight. In addition, blood TNF receptor levels have been shown to be inversely correlated to the percentage of body fat. In a similar manner, increased blood CRP levels have been shown to be related to resting energy expenditure and fat-free mass or body mass index. Appetite-regulating biomolecules, leptin and ghrelin, have also been related to body composition in COPD. Broekhuizen and colleagues [49,50] found that blood leptin levels were lower in cachectic COPD patients compared to non-cachectic, and plasma ghrelin was found to be significantly higher in underweight COPD patients. What is not known is whether these markers predict who will become cachectic, which would make them very useful as a clinical biomarker. Pulmonary hypertension is also a phenotypic feature of COPD, more typically in the latter stages of disease. Joppa and colleagues [51] found that patients with pulmonary hypertension had elevated blood levels of CRP and TNF- $\alpha$  and that CRP was an independent predictor of pulmonary systolic pressure. Since the diagnosis of pulmonary hypertension requires an echocardiogram, CRP measurements may prove to be useful at least in determining who to screen for pulmonary hypertension.

**Biomarkers of systemic involvement in stable COPD: do they exist? – No (Giorgio W. Canonica / Fulvio Braido, Genoa, Italy)**

Biomarkers are *ex-vivo* markers, i.e. they can be taken out of the body and measured. They are biological material that reflect a disease process (e.g. a biomarker for inflammation). COPD is characterized by chronic inflammation of the small airways and lung parenchyma, with the involvement of neutrophils, macrophages, CD8+ lymphocytes, many cytokines and chemokines. This inflammation is associated with fibrosis and the narrowing of small airways and with lung parenchyma destruction, resulting from the action of various proteinases. The number of CD8+ lymphocytes is correlated to the airways flow limitation.

Neutrophils have the most important role in COPD pathogenesis and macrophages can damage lung parenchyma by releasing protease and neutrophil chemoattractant factors such as IL-8 and leukotriene B<sub>4</sub> (LTB<sub>4</sub>). These cells can be activated by cigarette smoke and CD8 lymphocytes, which damage the lung by releasing TNF- $\alpha$ . Neutrophils release proteolytic enzymes, such as elastase, cathepsins, metalloproteinases, causing the tissue damage typical of emphysema. Inflammation activ-

ity of neutrophils, lymphocytes and macrophages depends on growth factors such as granulocyte macrophage colony stimulating factor (GM-CSF), which controls neutrophil survival.

The inflammatory cascade implicated in lung parenchyma destruction may spread to systemic level and induce further organ damage. However, it should be borne in mind that elderly subjects present comorbidities, and COPD concomitant diseases may be the cause of the increased biomarkers in these patients. COPD and congestive heart failure (CHF) are the two most frequent and severe chronic diseases. About 20% of patients mainly followed for COPD are also affected by CHF. Moreover, both COPD and CHF share old age and smoking as the main risk factors, and have in common chronic inflammation as the potential pathogenic mechanism. Compared to COPD, the diagnosis of heart failure is more complicated since it requires the integration of clinical, echocardiographic and circulating biomarker data. In other terms, we could erroneously attribute the increase of biomarkers to COPD, since we ignore the presence of concomitant pathologies such as CHF or obstructive sleep apnea syndrome (OSAS) in which there is an increase of mediators involved in the induction of organ damage. Cytokines IL-6 and IL-1 $\beta$  are able to trigger a systemic inflammatory response characterized by an increase in the circulating levels of leukocytes, platelets, proinflammatory and prothrombotic proteins. This complex response produces CRP, fibrinogen and other coagulation factors which are associated to fatal cardiovascular events but also to the bronchial tree remodeling present in COPD. No doubts exist about the presence of systemic inflammatory markers and their organ-related effects in COPD. Nevertheless, further investigation is required to clarify the source and meaning of the inflammatory process. In this context, the systemic role of lung-specific biomarkers, such as serum Clara cell protein (CC-16), surfactant protein (SP)-A, and SP-D, could be interesting.

**Biomarkers of systemic involvement in acute exacerbations of COPD: is there overwhelming evidence? – Yes (Wisla Wedzicha / John Hurst, London, United Kingdom)**

Exacerbations of COPD are episodes of increased symptoms that are associated with increased airway and systemic inflammation. COPD exacerbations are now recognized as an important outcome measure in COPD but they are heterogeneous and also seasonal events. COPD exacerbations are often triggered by respiratory viral infections [51], though they are also associated with bacteria, and exacerbations where both viruses and bacteria are isolated are more severe [52]. Thus there has been considerable interest in developing a biomarker to detect and follow the time course of COPD exacerbations. There is evidence that during a COPD exacerbation the systemic inflammatory response is related to the airway response [45] and thus a systemic marker should reflect the pathophysiological

changes associated with the exacerbation. Early studies showed that acute phase markers increased during exacerbations, e.g. systemic IL-6 and plasma fibrinogen increased significantly at exacerbation and these increases were greater in the presence of an infective trigger [54]. It is also possible that rises in these biomarkers can lead to increased cardiovascular risk with a COPD exacerbation. A large study utilizing a whole panel of biomarkers showed that the most selective biomarker was CRP but the change in CRP was not sufficiently sensitive or specific alone [44]. Sensitivity and specificity was increased by combining CRP with one of the major exacerbation symptoms (dyspnea, sputum purulence or increased sputum volume) that were recorded during the study. There were no direct relationships between biomarker concentrations and clinical indices of exacerbation severity. A recent study has suggested that serum amyloid protein (SAA) may also be useful as a biomarker of an exacerbation [55]. There is need for a biomarker to represent exacerbation recovery and this requires further research. However, in a recent study, it has been shown that the CRP measured at 14 days after the onset of an exacerbation was related to early exacerbation recurrence [56]. Thus there is an urgent need for novel markers of exacerbation that can reflect both the onset of the exacerbation and the recovery period.

**Biomarkers of systemic involvement in acute exacerbations of COPD: is there overwhelming evidence? – No (Antonio Anzueto, San Antonio, USA)**

The current GOLD guidelines recognize that the impact of COPD on an individual patient depends not just on the degree of airflow limitation, but also on the severity of symptoms (especially breathlessness and decreased exercise capacity), systemic effects, and any comorbidities the patient may have [17]. Furthermore, COPD should be managed as a systemic disorder, with careful attention paid to comorbidities and their effect on the patient's quality of life. The main concomitant conditions associated with COPD are skeletal muscle weakness, osteoporosis, heart failure, cardiac arrhythmias, ischemic heart disease, stroke, depression, cancer, etc. Recently, several investigators proposed that a common mechanism by which major risk factors such as smoking, hyperlipidemia, and obesity might lead to chronic disease is systemic inflammation [38]. Systemic inflammation may explain the development of chronic diseases such as COPD and its association with systemic and complex abnormalities affecting other organs. It has been suggested that persistent pulmonary inflammation promotes the release of pro-inflammatory chemokines and cytokines into the circulation. These mediators then stimulate various end-organs such as liver, adipose tissue and bone marrow, that will release excessive amounts of acute phase proteins, inflammatory cells and secondary cytokines into the circulation, and the result is a state of persistent low-grade systemic inflammation [24]. The main controversia

that exist today relate to whether or not the source of inflammation is in the respiratory system. There is increasing evidence that the functional impairment of airway-bronchial constriction that results in increased workload, hyperinflation and impaired respiratory muscle function is the main source of inflammation. Recent reports characterize the upregulation of pro-inflammatory cytokines in the intercostals and other respiratory muscles [57]. In theory, anti-inflammatory treatment should contribute to the reduction of exacerbations. Clinical studies that involve the use of long-acting bronchodilators, with or without inhaled corticosteroids, or surgical interventions such as lung volume reduction surgery (LVRS) have been associated with significant reduction in COPD exacerbation [58-60]. Therefore, COPD is a disease associated with multiple comorbid conditions, but the physiological consequences of airway obstruction, mainly hyperinflation, may be the main precipitating factor of the systemic inflammatory response seen in these patients [61,62].

**Is COPD a respiratory disease with prominent systemic implications or a systemic condition with pulmonary symptoms? – Rationale (Bartolome Celli, Boston, USA)**

Is COPD a disease or not? "Disease" signifies a morbid condition defined by objective, physical signs, subjective symptoms or mental states, or functional or structural disorder. In contrast, "syndrome" is defined as a set of symptoms or conditions that occur together and suggest the presence of a certain disease or increased probability of developing the disease. Based on these accepted definitions, COPD is a disease as it is based on an objective physical sign: airflow limitation.

COPD has a pathophysiological expression in the lung. The airflow limitation results from airways inflammation and remodeling often associated with parenchymal destruction and development of emphysema (most patients have both). However, in many patients the disease is associated with systemic manifestations that can effectively result in impaired functional capacity, worsening dyspnea, health related quality of life and increased mortality [12,58]. The best recognized manifestations include the presence of concomitant cardiovascular compromise, malnutrition involving primarily loss and dysfunction of skeletal muscles, osteoporosis, anemia, increased gastroesophageal reflux, and clinical depression and anxiety. Importantly, the presence of airflow limitation greatly increases the likelihood that a COPD patient may develop lung cancer over time. In addition, patients with COPD are older and frequently present with important comorbidities that require medical attention. Patients with milder COPD will likely die from diseases other than COPD but most patients with severe and very severe COPD die from COPD [12,63,64].

There are two different views relating the associations between COPD and its comorbidities: i) systemic "spillage" of the inflammatory and reparatory events occurs in the lungs, with the disease remain-

ing at the center of the process; ii) pulmonary manifestations of COPD are an expression of a "systemic" inflammatory state with multiple organ compromise. Both views have merit but imply different conceptual approaches with important therapeutic consequences. In the former, the aims of therapy are primarily centered in the lungs whereas in the latter the center of therapy is shifted to the primary source.

Medical and surgical therapies aimed at improving lung function have proven important in decreasing dyspnea, and improving exercise capacity, health status and even mortality [63,65-67]. Similarly, therapies such as oxygen for hypoxemic patients and pulmonary rehabilitation have also improved outcomes for patients without altering lung function significantly [10,17,70-73]. The next decades will see an explosion of information attempting to elucidate the associations between COPD and its systemic expressions, providing objective evidence of the mechanisms and, in the end, improving the management of patients with COPD.

**Is COPD a respiratory disease with prominent systemic implications or a systemic condition with pulmonary symptoms? - Case report (Richard ZuWallack, Hartford, USA)**

CG is a 75 year old woman with a diagnosis of COPD since approximately 1995. She has a 45 pack-year history of cigarette smoking, but quit at age 50. She has no history of asthma, atopy, or frequent childhood respiratory infections. At age 61 she began experiencing breathlessness with exertion. A diagnosis of COPD was made at that time, and she was initially treated with ipratropium, 2 inhalations, 4-times daily. During stable periods her chest examination reveals signs of hyperinflation, diminished breath sounds throughout, a prolonged expiratory phase, and no adventitious sounds. Data from her first pulmonary function evaluation in 1996 are as follows: age 64, weight 59 kg, body mass index (BMI) = 22 kg/m<sup>2</sup>, post-bronchodilator (FEV<sub>1</sub>/FVC) = 0.61, FEV<sub>1</sub> = 1.33 L (54% of predicted), carbon monoxide diffusing capacity (DLCO) = 49% of predicted, arterial blood gases while breathing room air: pH 7.42, PaO<sub>2</sub> 68 mm Hg, PaCO<sub>2</sub> 36 mm Hg. Her Medical Research Council (MRC) dyspnea rating (0 to 4 scale) was 1: troubled by shortness of breath when hurrying on the level or walking up a slight hill. Chest X-rays show hyperinflation, but no other abnormality. In the past 12 years, she has had approximately 2-3 COPD exacerbations per year, but was hospitalized only once, in 2003. She has had an unexplained, gradual decrease in body weight despite taking calorie supplements; her last recorded weight was 45 kg, BMI = 16.5 kg/m<sup>2</sup>. She could not tolerate megestrol because of increased dyspnea, and was reluctant to begin anabolic steroids. Documented comorbidities include a history of peptic ulcer disease, coronary artery disease, an asymptomatic ~50% left carotid artery stenosis, a dilated, probably non-ischemic cardiomyopathy (left ventricular ejection

fraction ~ 35%), paroxysmal atrial fibrillation treated with oral anticoagulation, migraine headaches, and a history of anxiety and depression. At her latest spirometry (2007) the FEV<sub>1</sub>/FVC was 0.42 and the FEV<sub>1</sub> was 0.91 L, or 41% of predicted. She is now MRC 3 (0-4 scale): stops for breath after walking about 100 yards or after a few minutes on the level. On exercise testing her peak exercise capacity on a cycle ergometer was 10.5 mL/kg/min, which was 50% of predicted. She was dyspnea-limited and did not have a discernable anaerobic threshold. There was no significant oxygen desaturation during exercise testing. Her latest respiratory medications include inhaled formoterol twice daily, tiotropium once-daily, and albuterol as needed.

CG has COPD which is of moderate-severe spirometric severity; historically, she has had relatively frequent respiratory exacerbations. She also has pulmonary cachexia, atherosclerosis, coronary artery disease, left ventricular disease, anxiety, and depression. One way of interpreting this constellation of medical problems is that COPD results from a local (respiratory) inflammatory response to environmental stimuli, such as cigarette smoke, and this respiratory inflammatory process has systemic, 'spill over' effects. This, in turn, causes other problems, such as cachexia and cardiovascular disease. This concept is implied in the description of COPD given by the ATS/ERS Statement on COPD [74], which states that COPD is characterized by inflammation in the lungs, and that this has systemic consequences. Another interpretation is that COPD is primarily a systemic disease in which the lung is the major target organ. The weight loss and the cardiovascular disease that CG has are both manifestations of the systemic abnormalities associated with COPD. Although not stated, she also likely has other systemic manifestations, such as peripheral muscular dysfunction and osteoporosis. The well-described correlation between COPD and cardiovascular disease is not surprising, since these two diseases are both strongly related to cigarette smoking. However, COPD itself is an important predictor and assumed risk factor for atherosclerosis and cardiovascular mortality [25,75-77]. Furthermore, this relationship remains even after controlling for cigarette smoking [78]. In general, a 10% decrease in FEV<sub>1</sub> in COPD patients is associated with approximately a 30% increase in risk of cardiovascular death [79]. Poor lung function is, in fact, a stronger predictor of cardiovascular and all-cause mortality than serum cholesterol [77]. From an analysis of data from the 3<sup>rd</sup> National Health and Nutrition Examination Survey (NHANES), individuals with moderate to severe airflow obstruction had increased circulating leukocyte and platelet counts, elevated fibrinogen levels, and were more likely to have elevations in CRP than those without obstruction [77]. Moderate and severe airflow obstruction was significantly associated with cardiac ischemia. Inhalation of ambient particulate air pollution also induces a low-grade systemic inflammation [80]. In one model of systemic inflammation in COPD [38],

the lungs are the portal for the entry of toxins (cigarette smoke and ambient particulate matter), which are processed by alveolar macrophages and epithelial cells. These cells produce proinflammatory mediators that promote inflammation in the lung. These mediators also translocate into the circulation and set up a systemic inflammatory response that includes: 1) stimulation of the bone marrow to release leukocytes and platelets, 2) activation of an acute phase response which includes the production of procoagulation factors, and 3) activation of the endothelium. These processes increase the likelihood of vascular disease. Other proinflammatory cytokines, such as TNF- $\alpha$  also promote body composition abnormalities such as depletion of lean body mass or even cachexia. It is clear that systemic inflammation is present in COPD and that this contributes directly to the lung disease and its co-morbidities. Whether this process is viewed as a systemic 'spill-over' from inflammation in the lung or is a primarily systemic process with the lung as the portal is, in reality, more semantic than pragmatic.

**Approach to COPD: respiratory or systemic treatment? - Respiratory approach (Richard Casaburi, Torrance, USA)**

Pharmaceutical companies continue to focus on developing new inhaled bronchodilator drugs, mostly in the classes already demonstrated to be effective: anticholinergic and  $\beta$ -agonist drugs. Inhaled corticosteroids remain very much part of the treatment paradigm. True, oral drugs are likely to re-emerge as treatments for COPD. Many are anti-inflammatories, but the target is the lung, not systemic inflammation. A number of mediator antagonists, antioxidants, signal transduction pathway inhibitors, proteinase inhibitors, mucoregulators, pulmonary vasodilators are under development [81]. Further in the future are agents that will induce lung parenchymal growth and repair, possibly including the therapeutic use of stem cells. Also to be considered are approaches to improve lung mechanics in emphysema, including LVRS and newer endobronchial valves and the airway fenestration and stenting procedures [82]. Clearly, the lungs are the dominant focus of therapies for COPD. Even treatments aimed at systemic manifestations of COPD are primarily aimed at relieving pulmonary limitations. Exercise programs that are part of pulmonary rehabilitation reverse dysfunction of the muscles of ambulation. However, the mechanism by which training programs improve exercise tolerance is largely through reduction of the dynamic hyperinflation related to reduced ventilatory demand at a given level of exercise [83].

While substantial attention has been placed on systemic inflammation in COPD, the increased levels of circulating inflammatory mediators reported in moderate-severe COPD [4] are small and of questionable importance. It has been difficult to predict patient characteristics that are reliably associated with the substantial increases in circulating inflammatory mediators that are likely to be important

(and, therefore, to constitute a good therapeutic target) in the individual patient. Moreover, to date it is not clear whether circulating inflammatory mediators are simply a "spill-over" from pulmonary inflammation or related to systemic production [34]. Similarly, muscle dysfunction has been ascribed, in part, to inflammation and apoptosis. However, the variability in these findings among subjects makes this a difficult therapeutic target.

**Approach to COPD: respiratory or systemic treatment? - Systemic approach (Leonardo M. Fabbri, Modena, Italy)**

The only treatment that affects COPD progression is smoking cessation [17]. Despite the inflammatory nature of COPD, no existing medication has been shown to modify the long-term decline in lung function. Hence the goals of COPD management are reduction of risk factors, management of stable COPD and its comorbidities, and prompt recognition and management of COPD exacerbations [17]. Smoking cessation is the most effective intervention to reduce the risk of development and the progression of COPD and reduce mortality.

Pharmacotherapy (nicotine replacement, bupropion, nortryptiline and/or varenicline) may help patients stop smoking. Also, occupational, indoor/outdoor pollution should be avoided. Pharmacologic treatment of COPD may improve symptoms, reduce frequency and severity of exacerbations, improve health status, and improve exercise tolerance. Albeit the mechanisms are poorly understood, inhaled  $\beta_2$ -agonists and/or anticholinergics are central to pharmacologic management in COPD, both on an as needed basis to relieve intermittent or worsening symptoms and on a regular basis. Non-pharmacologic treatments include rehabilitation, oxygen therapy, and surgical interventions [17]. The diagnosis, assessment of severity and treatment of COPD may be greatly affected by the presence of comorbid conditions. Lung function measurement, non-invasive assessment of left ventricular function (e.g. echocardiography and brain natriuretic peptide) and/or glycaemia, may be useful to identify these comorbidities. Similarly, smoking prevention and cessation, weight control and diet, and exercise and rehabilitation potentially affect not only COPD but also its comorbidities [24,34,43].

Pharmacological treatment of COPD chronic comorbidities is more complex, as drugs are usually developed for single diseases or organs [84]. Much can be learnt from other chronic conditions, e.g. diabetes. Glucose control with insulin and/or oral anti-diabetic agents not only controls diabetes but also helps prevent and treat the systemic effects and comorbidities of diabetes, particularly cardiovascular diseases [84]. More recently, drugs used for the treatment of erectile dysfunction, hypertension, chronic heart failure, or lipid disorders, have been shown to have unexpected beneficial effects in COPD patients. Statins, which are used primarily as lipid-lowering agents, have also potent anti-inflammatory properties in the lung and have been shown

to positively affect chronic comorbidities of metabolic syndrome, e.g. chronic heart failure, vascular diseases and COPD [84-86].  $\beta$ -blockers, considered life-saving drugs in chronic heart failure, have also been recently shown to provide benefits in COPD patients, albeit they may carry some risks in patients with an asthmatic component of COPD [87]. Beneficial effects have been reported for ACE inhibitors, and angiotensin receptor blockers [84]. On the other side, drugs specifically developed and used to treat COPD, e. g. inhaled bronchodilators [88,89] and inhaled steroids alone or in combination with inhaled bronchodilators [58,90-101], may have significant beneficial effects on cardiovascular diseases and other common chronic comorbidities of COPD.

#### **Guidelines and clinical practice: myth or reality? - Myth (Marc Miravittles, Barcelona, Spain)**

The debate on the clinical usefulness of some drugs in COPD, e.g. inhaled corticosteroids (IC), stems from the poor current definition of COPD as simply a syndrome with nothing whatsoever regarding its etiology [102]. The energy invested in identifying and quantifying the different "faces" of COPD, known as the diagram of Venn not proportional to COPD [103], while commendable, only demonstrates the confusion existing between the different etiopathogenic, clinical and morphological forms of the syndrome labelled COPD [104,105]. Due to the poor definition of COPD, patients with very different characteristics have been enrolled in different clinical trials, thereby producing a great variability in the response to treatment [106]. This aspect is fundamental if one wishes to compare results obtained with different drugs or with the same drugs across different studies. One more instance of the incongruence of the definition of COPD is the discrepancy between the universally accepted definition of the GOLD guidelines [107] and inclusion criteria of the clinical trials on COPD [58,108]. If COPD is what GOLD states, why not use this definition as the inclusion criteria for clinical trials? The answer is that what we understand COPD to be is only partly reflected in the definition. Until we adjust the definition to what we really understand COPD to be in clinical practice, sterile controversies will continue on the efficacy of different treatments for the so-called "COPD". One convincing test on the importance of carrying out a directed and not stepwise treatment may be found in a study performed by Siva et al. [109]. A total of 82 patients with COPD were randomized to two groups to receive treatment according to i) British Thoracic Society guidelines (BTS group), or ii) the eosinophilic inflammation observed in the induced sputum (sputum group). Patients in the sputum group were administered IC or oral drugs with the objective of maintaining the eosinophilic count in sputum < 3%. After 1 year, the strategy of the sputum group was associated with a 62% reduction in the number of severe exacerbations ( $p = 0.037$ ) versus those who were treated according to BTS guide-

lines, with no differences being observed in the use of oral corticosteroids between the two groups. These results indicate that to achieve greater treatment efficacy, we should be guided by the characteristics of the patients more than by their severity. We no longer have one treatment for COPD but rather - similar to what happens with other chronic diseases such as hypertension or diabetes - different therapeutic options that should be targeted to the individual patient. It is difficult to achieve a consistent definition of COPD and establish what is adequate treatment for the different types and subtypes described in this definition, but possible if we break through the taboos of the past.

#### **Guidelines and clinical practice: myth or reality? - Reality (Stephen Rennard, Omaha, USA)**

There are two situations in which guidelines are useful for the clinician. First, when diagnostic or therapeutic modalities are inappropriately used. Evidence suggests that the diagnosis of COPD, although straightforward and readily obtained by simple spirometry, is inadequately accomplished in both the USA and Europe [110,111]. As a result, many individuals with COPD are undiagnosed or, in the absence of spirometry, incorrectly diagnosed. Application of spirometry, as recommended by guidelines [17], would address this diagnostic issue. Similarly, rehabilitation in COPD is widely recommended by guidelines [112] but inadequately applied [113]. The availability of guidelines may help optimize application of appropriate therapies in a population. Second, guidelines can help provide a framework for the clinician when application of a diagnostic or therapeutic modality is uncertain, e.g. ICs have measurable benefits on airflow, exacerbation frequency and mortality in COPD [17] but how they should be used clinically requires discernment. Guidelines that use evidence when available and expert opinion when necessary can inform clinicians in making their judgments. Guidelines, therefore, can help optimize diagnosis and therapy and are therefore an important tool for the clinician.

#### **CONCLUSION**

Nikos Siafakas (Heraklion, Greece) in his summing up of the meeting stated that much energy and attention during the two-day Seminar had been focused on how to define the term 'systemic'. The first step was to agree on the definition. But first of all, was COPD a disease or a syndrome? He personally agreed with Marc Miravittles that COPD does fulfill the criterion for disease (i.e. it has a distinct cause-etiology) but it is one characterized by different faces or phenotypes. A vote was taken on this and there was a vast consensus that COPD was a disease (one vote only for syndrome). As to the real issue of the Seminar, i.e. whether COPD is a systemic disease or not, the next step was to agree on what 'systemic' means. During the Seminar, 'systemic' had been referred to in various senses, as: a) sys-

temic inflammation; b) systemic manifestations; c) systemic consequences; d) comorbidities (some confused these with systemic effects, e.g. if you have two diseases in common like diabetes and COPD there must be an overlap, but is this an overlap or cause & effect?); e) multi-organ disease. After lengthy discussion, a vote was taken and the large majority expressed their understanding of COPD as having 'systemic consequences', or 'systemic manifestations'. The issue remaining was to decide if these systemic manifestations of COPD imply a multi-organ disease (like scleroderma or lupus) or some more centrogenic disease followed by effects in sequence.

Carlo Grassi (Milan, Italy) in closing the Symposium confirmed that, while the Seminar had not reached a final evidence-based conclusion, a general consensus had emerged based on the limited evidence available: that COPD begins as chronic airways obstruction, dynamic hyperinflation and local inflammation in the lungs and from this leads - through differentiated pathways still to be clarified - to systemic consequences. The Seminar, Grassi said, would represent a starting point for a new era in clinical and experimental research, based on the excellent quality of the discussions held over the two days by the experts gathered in this unforgettable setting of Venice.

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