available at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/rmed

Neurological and endocrinological disorders: orphans in chronic obstructive pulmonary disease

Wolfram Doehner[a,b], Karl Georg Haeusler[a,c], Matthias Endres[a,c], Stefan D. Anker[b,d], William MacNee[e], Mitja Lainscak[b,f]

[a] *Center for Stroke Research Berlin, Charité Medical School, Berlin, Germany*
[b] *Applied Cachexia Research, Charité Universitaetsmedizin Berlin, Berlin, Germany*
[c] *Department of Neurology, Charité – University Medicine Berlin, Germany*
[d] *Center for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy*
[e] *MRC Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, Scotland, United Kingdom*
[f] *Division of Cardiology, University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia*

KEYWORDS
Chronic obstructive pulmonary disease;
Diabetes mellitus;
Insulin resistance;
Metabolic syndrome;
Stroke

Summary
Patients with chronic obstructive pulmonary disease (COPD) are often characterised by a range of characteristic co-morbidities that interfere with their pulmonary disease. In addition to a mere association with co-morbidities, a complex pathophysiological interaction and mutual augmentation occurs between COPD and its co-morbidities that may result in disease progression and increased morbidity and mortality. An interdisciplinary approach is required both for diagnosis and treatment to target co-morbidities early in the course of the disease. This review summarizes the current knowledge of the interaction with cerebrovascular disease and endocrinological co-morbidities in COPD patients.
There is growing evidence that COPD is an independent risk factor for ischemic stroke, increasing the risk about twofold. Stroke risk in COPD patients increases with the severity of the disease as measured by the degree of airflow limitation. The presence of cardiovascular risk factors is of particular importance for stroke prevention in COPD patients. Endocrinological co-morbidities are also important and many are associated with increased cardiovascular risk. Impaired glucose metabolism ranges from insulin resistance to overt diabetes mellitus, which is a frequent finding and is associated with worse outcome.

Introduction

Chronic obstructive pulmonary disease (COPD) reaches beyond the lungs, resulting in many systemic manifestations. Key mechanisms involved in the pathophysiology and systemic manifestations are hypoxaemia, hypercapnia, systemic inflammation, and neurohormonal activation.[1,2] A variety of co-morbidities in COPD patients influence the clinical presentation and patient outcomes.[3] Until relatively recently there was little attention paid in the literature to co-morbidities in COPD. Most published reports on co-morbidities focus on systemic inflammation, cancer, and cardiovascular disease while the body of evidence on cerebrovascular disease and glucose metabolism is much less. Clearly, an interdisciplinary approach is warranted in order to adequately target relevant risk factors and pathophysiological cross-links that may traditionally be considered as non-pulmonary medical issues. This review will summarize the available evidence for cerebrovascular and endocrinological complications and co-morbidities in COPD to provide critical evaluation of current knowledge, implications for clinical practice and to give guidance for future research.

* Corresponding author. Mitja Lainscak, MD, PhD, FESC. Assistant Professor of Internal Medicine, Division of Cardiology, University Clinic or Respiratory and Allergic Diseases Golnik, Golnik 36, SI-4204 Golnik, Slovenia.
Tel.: +386 31 379 533; Fax: +386 4 2569 117.
E-mail: mitja.lainscak@guest.arnes.si (M. Lainscak).

0954-6111$ – see front matter

Table 1
Mechanisms of increased stroke risk in patients with COPD.

Mechanism	Underlying cause	Reference(s)
↑ coagulation	↑ fibrinogen concentration	Pinol-Ripoll 2008[12]
	↑ thrombin-antithrombin complex level	Sabit 2010[19]
	↑ prothrombin activation fragments 1 & 2	Sabit 2010[19]
	↑ plasminogen activator inhibitor-1 level	Jiang 2010[20]
↑ thrombocyte aggregation	↑ β-thromboglobulin concentration	Cella 2001[23]
	↑ P-selectin level	Davì 1997[24]
	↑ thromboxane biosynthesis	
↑ endothelial dysfunction	↓ nitric oxide concentration	Cella 2001[23]
	↑ thrombomodulin concentration	Cella 2001[23]
	↓ flow-mediated vasodilation	Eickhoff 2008[21]
	↑ arterial stiffness	Maclay 2009[22]
↑ large artery atherosclerosis	↑ oxidative stress	Fimognari 2008[17]
	↑ C-reactive protein levels	
↑ small vessel occlusion	↑ prevalence of diabetes	Feary 2010[8]
? borderzone infarction	↓ lower arterial oxygen pressure & reduced cerebral blood flow	Miyamoto 2000,[25] van Dijk 2004[26]

Cerebrovascular disease

Stroke as a consequence of COPD

The growing prevalence of cardiovascular risk factors is an increasing medical and socioeconomic problem in modern society. Importantly, with improved medical care of acute cardiovascular events and an increasingly aged society the prevalence of chronic diseases will increase and contribute to an increasing prevalence of co-morbidities such as COPD and stroke. Various interrelated mechanisms contribute to an increased stroke risk in COPD-patients. First, COPD and stroke may co-exist as a result of shared risk factors. The probability of cardiovascular disease is much higher in COPD-patients. According to data from the American National Health Interview Survey (NHIS; n = 18,342; aged ⩾40 years) the odds ratio for cardiovascular disease was 2.7 (95% CI 2.3–3.2) for COPD-patients,[4] including a higher risk for established stroke risk factors like myocardial infarction (OR 2.2 (95% CI 1.7–2.8)),[5] congestive heart failure (OR 3.9 (95% CI 2.8–5.5))[6] and cardiac arrhythmia (OR 2.4 (95% CI 2.0–2.8)).[7] Similar results were reported from a large UK-database (The Health Improvement Network, THIN), of 1,200,000 medical records from over 300 primary care centres. In this study there was an OR of 5.0 (95% CI 4.9–5.8) for cardiovascular disease, and an OR of 2.0 (95% CI 2.0–2.1) for diabetes in physician-diagnosed COPD-patients.[8] A retrospective analysis of medical records from Saskatchewan (Canada) revealed a significantly higher rate of myocardial infarction (OR 1.6, 95% CI 1.4–1.8), congestive heart failure (OR 3.8, 95% CI 3.6–4.1) and cardiac arrhythmia (OR 1.8, 95% CI 1.6–1.9) in COPD-patients.[9] Subsequently, patients with COPD are at risk of stroke due to large-artery atherosclerosis, small-vessel occlusion and embolic stroke.

Furthermore, available data indicate, that COPD poses a direct increased risk for stroke in addition to shared risk factors for both diseases. According to THIN-data, COPD increases the odds of having a stroke (including subarachnoid and intracranial hemorrhage and transient ischemic attack (TIA) by 3.3 (95% CI 3.2–3.5) or 2.8 (95% CI 2.6–3.0) for first-ever stroke, respectively[8]. In addition, the NHIS-data indicated an OR of 1.5 (95% CI 1.1–2.1) for stroke in COPD-patients[4], which is in line with a report from the prospective Atherosclerosis Risk in Communities (ARIC) study, which reported an adjusted HR of 1.50 (95% CI 1.04–2.2) for stroke in patients with or without asthma.[10] In addition in the Saskatchewan cohort, there was a significantly higher rate of stroke (OR 1.1 (95% CI 1.02–1.2)) in COPD-patients[9]. A German case–control study (including 370 patients with mild to moderate stroke as well as age- and gender-matched controls) demonstrated an OR of 2.6 (95% CI 1.2–5.9) for stroke in patients with self reported moderate to severe chronic bronchitis (CB).[11] Unfortunately, this study was underpowered to detect independent associations between CB-patients and TIA or hemorrhagic stroke. Finally, a Spanish case–control study (including 393 stroke patients) revealed an OR of 1.8 (95% CI 1.4–2.5) for stroke in patients with self-reported CB.[12]

The mechanisms for the association between COPD and stroke are not fully understood, however several possible mechanisms have been proposed. First, COPD is a chronic inflammatory condition with an association with acute and chronic infections,[13] and inflammation/infection is *per se* a proven risk factor for ischemic stroke.[14] Inflammation/Infection promotes large-artery atherosclerosis[15–17] and induces a pro-coagulatory state leading to thrombus formation and embolic stroke.[18] In addition, there is evidence for enhanced atherosclerosis, hypoxia-induced systemic oxidative stress[17] and hypercoagulability,[19,20] endothelial dysfunction,[20,21] arterial stiffness[22] and increased thrombocyte aggregation in COPD-patients[23,24] – Table 1. COPD is associated with overactivity of the sympathetic nervous system and of the renin–angiotensin–aldosterone system,[27] which seems to be of particular importance in this regard. Similar pathophysiological changes have been

described for obstructive sleep apnoea,[28] which is a known risk factor of ischemic stroke.[29] Despite the fact that the frequency of obstructive sleep apnoea in COPD-patients is similar to the general population, both disorders ("overlap syndrome") coexist in about 1% of all male adults, leading to more pronounced nocturnal oxygen desaturation[28] Also for muscle tissue wasting and structural muscle changes an overlap between stroke[30] and COPD[31,32] may exist. Whether this myopenia[33] is disease specific or results from a common and/or additive catabolic overdrive[34] remains to be established.

Prevalence and incidence of stroke in patients with COPD

Data from the NHIS[4] indicate that 8.0% of all COPD-patients (n = 958; mean age 63 years, 56% female) had a history of stroke before enrolment. In this study the ethnical background or the body mass index had no impact on stroke risk in COPD-patients. By contrast gender was a significant confounder as stroke was more prevalent in men than in women in the NHIS (OR 1.3 (95% CI: 1.1–1.7))[4]. A similar gender-related stroke rate was reported in the THIN data set.[8] As expected, multivariable analysis of THIN-data identified advanced age and smoking as additional stroke risk factors in patients with COPD. However, during a median follow-up of 895 days the incidence of first-ever stroke was highest in the younger age groups (HR 3.44 (95% CI 0.85–13.8) and HR 2.21 (95% CI 1.3–3.6) for 35–44 or 45–54 years, respectively).[8]

The stroke risk is also dependent on the disease severity of COPD as suggested by the majority of observational studies.[35] However, only two studies[35,36] corrected for relevant confounders such as smoking, socioeconomic status or diabetes. According to both studies, there was an almost linear association between the decrease of forced expiratory volume and ischemic stroke risk.

White matter lesions and silent stroke in patients with COPD

White matter lesions are frequently detected in older individuals[37] as a consequence of cerebral arteriosclerosis, hypoperfusion and focal ischemia.[38] One might argue that lower arterial oxygen tensions in COPD-patients may augment white matter lesions. However, hypoxia without additional ischemia did not cause brain necrosis in rats, although hypoxia exacerbates ischemic damage.[25]

There are a limited number of observational studies that have focused on brain MRI findings in patients with COPD. The Rotterdam Scan study reported MRI-detected silent strokes in about 20% of all 1077 non-demented participants aged 60–90 years.[37] A subgroup analysis focused on 73 individuals with COPD[26]). Compared to participants without COPD those with COPD had significantly more severe white matter lesions within the periventricular arterial border zone, indicating that cerebral hypoperfusion might play a role. Similar results were obtained for participants with lower arterial oxygen saturation, which suggests that hypoxemia is an important factor. There was no relevant increase in subcortical lesions or lacunar strokes in participants with COPD. Interestingly, the smoking status of COPD-patients did not affect this association.

A subgroup analysis of the Atherosclerosis Risk in Communities Study assessed lung function and brain MRI in 1917 patients (aged 55–72 years, 50% African-Americans) without a history of a stroke.[38] Compared with the highest FEV-quartile, patients in the lowest quartile had a threefold higher rate of clinically silent stroke and a twofold higher risk of white matter disease. Within the lowest FEV-quartile 20% had a silent stroke and 16% had white matter lesions. Furthermore, the results of the Cardiovascular Health Study emphasise the link between the severity of COPD and white matter lesions.[39] However, the association between lower FEV_1 and the extent of white matter lesions was not significant after adjustment for gender and history of smoking.

In the Cardiovascular Health Study, about one third of all 3301 participants without a history of stroke (aged 65 years and older) had a clinically silent stroke according to MRI findings. Unfortunately, MRI data for patients with known COPD were not reported.

A case–control study with small numbers of cases (18 COPD-patients, 9 age- and gender-matched controls) using MRI and MRI spectroscopy did not find relevant structural alterations (such as hippocampal atrophy or enhanced white matter lesions) or significant neurochemical brain changes.[40] According to a recent meta-analysis, white matter lesions generally predict an increased risk of dementia, stroke, and death.[41] Comparable data for white matter lesions in COPD-patients are missing so far. Whether white matter lesions are linked to cognitive impairment in patients with COPD is not known at present. However, up to 77% of all patients with COPD and hypoxemia experience neuropsychological changes including decreased attention, loss of memory, diminished psychomotor speed and decreased executive function,[42] findings similar to those described for patients with chronic heart failure.[43] Moreover, existing cognitive impairment obviously predicts mortality in COPD-patients.[42]

Stroke and COPD: Implications for mortality

Recent evidence indicates a higher (cardiovascular) mortality after ischemic stroke in patients with COPD[9]. About 4% of all COPD-related deaths within the "Towards a Revolution in COPD Health" (TORCH) study were caused by stroke.[44] In addition, a history of in-hospital stroke was independently associated with a significantly higher in hospital mortality in a cohort of 398 patients hospitalized for COPD exacerbations.[45] Moreover, the risk of stroke-associated death has been shown to be inversely related to FEV.[46]

Acute stroke therapy and stroke prevention in COPD-patients

Currently, there is no convincing evidence that provision of oxygen is effective after acute stroke in humans.[47] However, animal data support the concept of normobaric hyperoxia for neuroprotection after acute stroke.[48] The current European Stroke Organisation (ESO) guidelines state that "treatment of hypoxia is believed to be important

in individuals with extensive brain stem or hemispheric stroke, seizure activity, or complications such as pneumonia, cardiac failure, pulmonary embolism, or exacerbation of COPD".[49]

Available evidence on the prevention of strokes in COPD-patients is limited. According to guidelines the presence of COPD is not relevant for primary or secondary stroke prevention.[49] Therefore, stroke prevention in COPD-patients has to be tailored according to their cardiovascular risk profile. Anticoagulation is only indicated in COPD-patients with atrial fibrillation and not in those with sinus rhythm.[50] Apart from smoking cessation, treatment of additional cardiovascular risk factors is of particular importance in COPD-patients.

Clinical implications

COPD is an independent risk factor for stroke, increasing the stroke risk by around twofold. Moreover, stroke-related mortality rates are considerably higher in COPD-patients. Stroke prevention in patients with COPD has to be tailored according to the existing cardiovascular risk profile. Prospective clinical studies are needed to test whether optimal treatment of COPD might reduce the burden of stroke.

Endocrinological issues in COPD

Chronic diseases often induce (over-)activation of several pathways, which disturb endocrinological homeostasis. A range of mechanisms including systemic inflammation, neurohormones, blood gas disturbances, and glucocorticoid administration contribute to anabolic/catabolic imbalance and impaired whole body metabolism in COPD. COPD is associated in some patients with muscle wasting and weakness, and thus many reports focused on anabolic hormones, thyroid function, and adrenal gland.[51,52] Together with neurohormonal activation[2,27,53] these factors promote catabolic dominance and hence the development of cachexia and it is in such patients that the most severe endocrinological disturbances occur. Although of primary interest in general healthcare, glucose metabolism and the metabolic syndrome have been less investigated in COPD.

Definitions

Type II diabetes mellitus (DM) is a typical disease of modern society such that it results from an unhealthy lifestyle.[54,55] Current diagnostic criteria primarily address blood glucose levels (fasting blood glucose, oral glucose tolerance test; $HbA1_c$) but in the clinical practice we identify only the tip of the iceberg with respect to disturbed glucose metabolism.[56] Insulin resistance (IR) is the underlying pathophysiological principle of type II DM and is defined as an impaired physiological response of glucose utilisation to a given insulin concentration. IR may initially be overcome by increased beta cell activity to increase endogenous insulin production. Accordingly, IR precedes clinically manifest DM by years, if not decades. Insulin is a hormone with pleiotropic actions that may be affected differently depending on whether there is reduced activity (if resistance applies) or increased stimulation (if hyperinsulinaemia provokes increased signalling) with consequent adverse effects on the cardiovascular, muscular, and metabolic systems. In COPD, an increased cardiovascular mortality risk seems most relevant and is associated with impaired glucose metabolism.[3] Screening for insulin resistance in clinical practice is done by an evaluation of metabolic syndrome criteria (Table 2). There is some dispute in the scientific community over these criteria[57-59] and it remains unclear whether they apply for patients with established chronic conditions, e.g. COPD or chronic heart failure.[60] While the features of the metabolic syndrome give an indirect indication of the presence of IR, direct measurement is less well established in routine clinical practice. A range of methods for quantification of IR are used, mainly in research studies that include single-point estimates or serial assessments of glucose/insulin in response to glucose or insulin stress. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is the most simple method which requires measurements of fasting plasma glucose and insulin. Comparable methods are Fasting Insulin Resistance Index (FIRI) and the QUick Insulin Check Index (QUICKI). More complex methods such as minimal modelling techniques require repeated blood sampling for glucose and insulin determination after intravenous application of glucose or insulin.[61] The Gold standard test is the euglycemic hyperinsulinemic clamp technique, which measures glucose turnover in a euglycemic steady state during high-level insulin infusion.

Table 2
Metabolic syndrome definition criteria.

	NCEP ATP III 3 out of 5	IDF waist + 2 out of 4
Waist circumference		
Males	$\geqslant$102 cm	$\geqslant$94 cm
Females	$\geqslant$88 cm	$\geqslant$80 cm
Fasting glucose[a b]	$\geqslant$5.6 mmol/L	$\geqslant$5.6 mmol/L
High density lipoproteins[b]		
Males	<1 mmol/L	<1 mmol/L
Females	<1.3 mmol/L	<1.3 mmol/L
Triglycerides[b]	$\geqslant$1.7 mmol/L	$\geqslant$1.7 mmol/L
Blood pressure[b]	$\geqslant$130/85 mmHg	$\geqslant$130/85 mmHg

NCEP ATP III: National Cholesterol Education Program Adult Treatment Pannel III; IDF: International Diabetes Federation.
[a] either above cut-off or established diabetes mellitus or specific treatment.
[b] either above cut-off or specific treatment.

Insulin resistance and the metabolic syndrome

In chronic diseases, several mechanisms can induce the resistance of peripheral tissues, particularly muscle and fat, to insulin. In relation to COPD cigarette smoking also induces chronic systemic inflammation and oxidative stress which increases risk of insulin resistance. An association between systemic inflammation and insulin resistance was demonstrated in a study that compared 56 patients with COPD and 29 healthy subjects.[62] HOMA-IR was significantly higher in COPD patients (1.68 ± 2.58 vs 1.13 ± 2.02, $p = 0.032$)

and correlated with serum levels of interleukin-6 ($r = 0.276$, $p = 0.039$) and tumour necrosis factor α ($r = 0.351$, $p = 0.008$). A significantly higher HOMA-IR was reported in another study[63] which compared 55 patients with COPD and 25 healthy controls ($p = 0.001$). Other reports found no such association but they included fewer patients, used oral glucose tolerance test or did not measure glucose uptake by stable isotopes.[64]

The definition of the metabolic syndrome is based on different criteria, which cluster around insulin resistance. In 200 patients with established chronic bronchitis or COPD, the prevalence of the metabolic syndrome was 47.5% and decreased with increasing severity of COPD. The presence of the metabolic syndrome was associated with increased levels of hs-CRP and interleukin-6 levels, independent of lung function impairment.[65] A population based survey in China detected airflow obstruction in 6.7% of 7358 adults and 20% of those complied with International Diabetes Federation metabolic syndrome criteria.[66] The prevalence is very likely underestimated because these criteria need to be adjusted for Chinese population. More important, however, is the finding that the adjusted risk of metabolic syndrome was higher in those with airflow obstruction than in those without (odds ratio 1.47, 95% confidence interval (CI) 1.12–1.92). When analysing the individual components of the metabolic syndrome, only central obesity (adjusted for body mass index) was significantly associated with airflow obstruction (odds ratio 1.43; 95% confidence interval 1.09–1.88). In summary of available evidence, the metabolic syndrome is common in COPD, may in part explain the increased risk of cardiovascular diseases in COPD, and should be actively screened for and managed in clinical practice.

Diabetes mellitus

Whilst information on insulin resistance and its relevance in COPD remains scarce, there are more data available for DM. Notably, as IR precedes frank DM by several years, the pathophysiologic mechanisms discussed above are active long before DM is clinically recognised in COPD patients. The use of systemic but not of inhaled glucocorticoids in COPD is associated with higher risk of developing diabetes.[67] The overall prevalence of DM in COPD is estimated to be 10–14%.[52] Whether COPD promotes development of DM is controversial. No such association was found in the Framingham Heart Study[68] and the National Health and Nutrition Examination Survey.[69] By contrast, an analysis of 5498 patients with COPD (530 in GOLD stage III/IV) showed increasing prevalence of DM with increasing GOLD stage (10.1% in I vs 14.5% in III/IV, odds ratio for GOLD III/IV vs I: 1.5 (95% confidence interval 1.1–1.9)). Additionally, there was a higher risk for hospitalization and death in COPD patients with concomitant DM.[70] Similar associations were found during hospitalization for exacerbation of COPD.[71] An analysis of 172 patients with exacerbations reported that DM occurred in 22% of patients and tended to increase mortality (adjusted hazard ratio 1.93, 95% confidence interval 0.43–8.64).

Management

Conventional treatment of impaired glucose metabolism primarily focuses on increased insulin dose rather than insulin effectiveness. The most commonly used oral pharmacological antidiabetic agents act as promotors of endogenous insulin secretion whilst insulin is available as for parenteral or nasal treatment.[72] Metformin is another oral antidiabetic agent which serves as an insulin sensitizer and has the potential to reduce insulin resistance. Preliminary data from a group of 61 patients with COPD and DM suggest that in addition to their effects on glucose metabolism, insulin sensitizers have the potential to improve pulmonary function.[73] Several interventions with potential outcome benefit in patients with COPD could also improve glucose metabolism through demonstrated ancillary effects. Several of these, like exercise training, testosterone, and beta blockers, have been shown to reduce insulin resistance, likely through their actions in skeletal muscle and fat tissue.

Clinical implications

Active screening, primarily for sub clinical diabetes, and timely management is warranted in COPD patients. Patients with COPD are regularly exposed to the medical system, either during stable phases of the disease in the outpatient clinic or in exacerbations requiring hospital admission. Both scenarios provide an opportunity to perform simple, inexpensive, and mostly reliable tests for the presence of endocrinological disorders. Because of established or potential prognostic implications, tests could include fasting blood glucose, oral glucose tolerance test, lipid and thyroid hormone profile. Although cardiovascular disease, DM, and other co-morbidities are established prognostic risk factor in COPD, there are no evidence based management guidelines for COPD patients with co-morbidities.[1,2] Currently it seems appropriate to consult co-morbidity specific guidelines. Muscle wasting and cachexia are not uncommon and are associated with reverse epidemiology. Based on previous experience in COPD and other chronic disease, some parameters like body size[74] or lipid profile[75] may be particularly important and should be considered to guide management.

Future research

There is a need for good epidemiological data on the prevalence and incidence of cerebrovascular disease and endocrinological disturbances in patients with COPD. Large-scale multicenter prospective observational surveys are of utmost importance in this regard. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)[76] included 2164 clinically stable COPD patients, 337 smokers with normal lung function and 245 never smokers. This database has a wealth of information and is expected to serve as basis for detailed analyses in this field. We should also make use of the existing patient databases, both in hospitalized and ambulatory patients. Due to selection bias, analyses of randomized trials are likely to be less relevant for clinical practice as they reflect only selected populations, often without the relevant co-morbidities discussed here. Initial analyses should include simple measures that could be implemented during 5-minute clinical consultation. Body size, routine laboratory measures, electrocardiogram, and different questionnaires have attractive cost-benefit ratios and could

provide relevant information on co-morbidities on a short notice.

Many patients with COPD die out of hospitals thus determination of cause of death remains extremely difficult.[77] Sudden cardiac death, cerebrovascular incidents, and respiratory failure may be most important causes of death[3] and some patients are likely to enter the medical system via specialized emergency rooms. Data Inquiry from stroke and acute coronary syndrome registries should be the first step to determine prevalence of acute events.

Although there is paucity of adequate epidemiological data, we should now consider interventional trials to address the targeted management of co-morbidities in COPD.[2] The authors firmly believe the time for adequately designed and performed (pilot) trials has come and some are already ongoing. We look forward to future reports to provide additional insight into the epidemiology and management of the somewhat neglected co-morbidities in patients with COPD.

Conflict of interest statement

The authors declare that they have no competing interest.

Funding

ML received the Heart Failure Association Research Fellowship. WD, KGH and ME received funding from the Federal Ministry of Education and Research via the Center for Stroke Research Berlin (01 EO 0801). WD received funding from the Verein der Freunde und Förderer der Berliner Charité. ME received support from the Volkswagen-Stiftung, Deutsche Forschungsgemeinschaft and the European Union.

References

1. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009;**33**:1165–85.
2. Doehner W, von Haehling S, Anker SD, Lainscak M. Neurohormonal activation and inflammation in chronic cardiopulmonary disease: a brief systematic review. *Wien Klin Wochenschr* 2009;**121**:293–6.
3. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006;**28**:1245–57.
4. Finkelstein J, Cha E, Scharf SM. Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. *Int J Chron Obstruct Pulmon Dis* 2009;**4**:337–49.
5. Loh E, Sutton MS, Wun CC, Rouleau JL, Flaker GC, Gottlieb SS, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med* 1997;**336**:251–7.
6. Pullicino PM, Halperin JL, Thompson JL. Stroke in patients with heart failure and reduced left ventricular ejection fraction. *Neurology* 2000;**54**:288–94.
7. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation is an independent risk factor for stroke: The Framingham study. *Stroke* 1991;**22**:983–8.
8. Feary JR, Rodrigues LC, Smith CJ, Hubbard RB, Gibson JE. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010;**65**:956–62.
9. Curkendall SM, DeLuise C, Jones JK, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006;**16**:63–70.
10. Schanen JG, Iribarren C, Shahar E, Punjabi NM, Rich SS, Sorlie PD, et al. Asthma and incident cardiovascular disease: the Atherosclerosis Risk in Communities Study. *Thorax* 2005;**60**:633–8.
11. Grau AJ, Preusch MR, Palm F, Lichy C, Becher H, Buggle F. Association of symptoms of chronic bronchitis and frequent flu-like illnesses with stroke. *Stroke* 2009;**40**:3206–10.
12. Pinol-Ripoll G, de la Puerta I, Santos S, Purroy F, Mostacero E. Chronic bronchitis and acute infections as new risk factors for ischemic stroke and the lack of protection offered by the influenza vaccination. *Cerebrovasc Dis* 2008;**26**:339–47.
13. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005;**2**:8–11.
14. Emsley HC, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. *Lancet Neurol* 2008;**7**:341–53.
15. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med* 1999;**340**:115–26.
16. Park YB, Ahn CW, Choi HK, Lee SH, In BH, Lee HC, et al. Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. *Arthritis Rheum* 2002;**46**:1714–9.
17. Fimognari FL, Scarlata S, Conte ME, Incalzi RA. Mechanisms of atherothrombosis in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2008;**3**:89–96.
18. Lindsberg PJ, Grau AJ. Inflammation and infections as risk factors for ischemic stroke. *Stroke* 2003;**34**:2518–32.
19. Sabit R, Thomas P, Shale DJ, Collins P, Linnane SJ. The effects of hypoxia on markers of coagulation and systemic inflammation in patients with chronic obstructive pulmonary disease. *Chest* 2010 2010;**138**:47–51.
20. Jiang Y, Xiao W, Zhang Y, Xing Y. Urokinase-type plasminogen activator system and human cationic antimicrobial protein 18 in serum and induced sputum of patients with chronic obstructive pulmonary disease. *Respirology* 2010;**15**:939–46.
21. Eickhoff P,Valipour A, Kiss D, Schreder M, Cekici L, Geyer K, et al. Determinants of Systemic Vascular Function in Patients with Stable Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2008;**178**:1211–8.
22. Maclay JD, McAllister DA, Mills NL, Paterson FP, Ludlam CA, Drost EM, Newby DE, Macnee W. Vascular dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; **180**:513–20.
23. Cella G, Sbarai A, Mazzaro G, Vanzo B, Romano S, Hoppensteadt T, et al. Plasma markers of endothelial dysfunction in chronic obstructive pulmonary disease. *Clin Appl Thromb Hemost* 2001;**7**:205–8.
24. Davì G, Basili S, Vieri M, Cipollone F, Santarone S, Alessandri C, et al. Enhanced thromboxane biosynthesis in patients with chronic obstructive pulmonary disease. The Chronic Obstructive Bronchitis and Haemostasis Study Group. *Am J Respir Crit Care Med* 1997;**156**:1794–9.
25. Miyamoto O, Auer RN. Hypoxia, hyperoxia, ischemia, and brain necrosis. *Neurology* 2000;**54**:362–71.
26. van Dijk EJ, Vermeer SE, de Groot JC, van de Minkelis J, Prins ND, et al. Arterial oxygen saturation, COPD, and cerebral small vessel disease. *J Neurol Neurosurg Psychiatry* 2004;**75**:733–6.
27. Andreas S, Anker SD, Scanlon PD, Somers V. Neurohormonal activation as a link to systemic manifestations of chrojnic lung disease. *Chest* 2005;**128**:3618–24.
28. McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease. *Am J Respir Crit Care Med* 2009;**180**:692–700.
29. Arzt M, Young T, Finn L, et al. Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med* 2005;**172**:1447–51.

30. Scherbakov N, Doehner W. Sarcopenia in stroke – facts and numbers on muscle loss accounting for disability after stroke. *J Cachexia Sarcopenia Muscle* 2011;**2**:5–8.
31. Koehler F, Doehner W, Hoernig S, Witt C, Anker SD, John M. Anorexia in chronic obstructive pulmonary disease–association to cachexia and hormonal derangement. *Int J Cardiol* 2007; **119**:83–9.
32. Franssen FM, Sauerwein HP, Rutten EP, Wouters EF, Schols AM. Whole-body resting and exercise-induced lipolysis in sarcopenic (corrected) patients with COPD. *Eur Respir J* 2008;**32**:1466–71.
33. Fearon K, Evans WJ, Anker SD. Myopenia—a new universal term. *J Cachexia Sarcopenia Muscle* 2011;**2**:1–3.
34. Scherbakov N, Dirnagl U, Doehner W. Body weight after stroke: Lessons from the obesity paradox. *Stroke* 2011;42. doi: 10.1161.
35. Hozawa A, Billings JL, Shahar E, Ohira T, Rosamond WD, Folsom AR. Lung function and ischemic stroke incidence: the Atherosclerosis Risk in Communities study. *Chest* 2006;**130**: 1642–9.
36. Truelsen T, Prescott E, Lange P, Schnohr P, Boysen G. Lung function and risk of fatal and non-fatal stroke. The Copenhagen City Heart Study. *Int J Epidemiol* 2001;**30**:145–151.
37. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM; Rotterdam Scan Study.Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke* 2003;**34**:1126–9.
38. Liao D, Higgins M, Bryan NR, Eigenbrodt ML, Chambless LE, Lamar V, et al. Lower pulmonary function and cerebral subclinical abnormalities detected by MRI: the Atherosclerosis Risk in Communities study. *Chest* 1999;**116**:150–6.
39. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke* 1996;**27**:1274–82.
40. Borson S, Scanlan J, Friedman S, Zuhr E, Fields J, Aylward E, et al. Modeling the impact of COPD on the brain. *Int J Chron Obstruct Pulmon Dis* 2008;**3**:429–34.
41. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2010;**341**:c3666.
42. Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. *Eur Respir J* 2010;**35**:913–22.
43. Pressler SJ. Cognitive functioning and chronic heart failure: a review of the literature. *J Cardiovasc Nurs* 2008;**23**:239–49.
44. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007;**62**: 411–5.
45. Roca B, Almagro P, López F, Cabrera FJ, Montero L, Morchón D, et al.; for the ECCO Working Group on COPD, Spanish Society of Internal Medicine. Factors associated with mortality in patients with exacerbation of chronic obstructive pulmonary disease hospitalized in General Medicine departments. *Intern Emerg Med* 2011;**6**:47–54.
46. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996;**313**:711–6.
47. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke* 1999;**30**:2033–7.
48. Shin HK, Dunn AK, Jones PB, Boas DA, Lo EH, Moskowitz MA, et al. Normobaric hyperoxia improves cerebral blood flow and oxygenation, and inhibits peri-infarct depolarizations in experimental focal ischaemia. *Brain* 2007;**130**:1631–42.
49. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;**25**:457–507.
50. Lainscak M, Dagres N, Filippatos GS, Anker SD, Kremastinos DT. Atrial fibrillation in chronic non-cardiac disease: where do we stand? *Int J Cardiol* 2008;**128**:311–5.
51. Creutzberg EC, Casaburi R. Endocrinological disturbances in chronic obstructive pulmonary disease. *Eur Respir J* 2003;**22**(Suppl 46):76s-80s.
52. Laghi F, Adiguzel N, Tobin MJ. Endocrinological derangements in COPD. *Eur Respir J* 2009;**34**:975–96.
53. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008;**31**:204–12.
54. Mozaffarian D, Kamineni A, Carnethon M, Djoussé L, Mukamal KJ, Siscovick D. Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study. *Arch Intern Med* 2009;**169**:798–807.
55. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ. Type 2 diabetes in children and adolescents. *Pediatr Diabetes* 2009;**10**(Suppl 12):17–32.
56. Meigs JB. Epidemiology of type 2 diabetes and cardiovascular disease: translation from population to prevention: the Kelly West award lecture 2009 Diabetes Care 2010;**33**:1865–71.
57. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006;**23**:469–80.
58. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant D, for the Conference Participants. Definition of metabolic syndrome: report of the National, Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;**109**:433–38.
59. Federspil G, Nisoli E, Vettor R. A critical reflection on the definition of metabolic syndrome. *Pharmacol Res* 2006;**53**:449–56.
60. Lainscak M, Doehner W, Anker SD. Metabolic disturbances in chronic heart failure: a case for the "macho" approach with testosterone?! Eur J Heart Fail 2007;**9**:2–3.
61. Doehner W, Anker SD, Godsland IF. Optimizing insulin sensitivity assessment using the minimal model in chronic heart failure. *Horm Metab Res* 2005;**37**:106–10.
62. Bolton CE, Evans M, Ionescu AA, Edwards SM, Morris RHK, Dunseath G, et al. Insulin resistance and inflammation – a further systemic complication of COPD. *COPD* 2007;**4**:121–6.
63. Eker S, Ayaz L, Tamer L, Ulubas B. Leptin, visfatin, insulin resistance, and body composition change in chronic obstructive pulmonary disease. *Scand J Clin Lab Invest* 2010;**70**:40–4.
64. Sauerwein HP, Schols AMWJ. Glucose metabolism in chronic lung disease. *Clin Nutr* 2002;**21**:367–71.
65. Watz H, Waschki B, Kirsten A, Müller KC, Kretschmar G, et al. The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* 2009;**136**:1039–46.
66. Lam KB, Jordan RE, Jiang CQ, Thomas GN, Miller MR, Zhang WS, et al. Airflow obstruction and metabolic syndrome: the Guangzhou Biobank Cohort Study. *Eur Respir J* 2010;**35**:317–23.
67. Walters JA, Walters EH, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;**3**: CD005374.
68. Walter RE, Beiser A, Givelber RJ, O'Connor GT, Gottlieb DJ. Association between glycemic state and lung function: the Framingham Heart Study. *AM J Respir Crit Care Med* 2003;**167**:911–6.
69. Ford ES, Mannino DM. Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Diabetes Care* 2004;**27**:2966–70.
70. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and

outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;**32**:962–9.
71. Parappil A, Depczynski B, Collett P, Marks GB. Effect of comorbid diabetes on length of stay and risk of death in patients addmitted with acute exacerbations of COPD. *Respirology* 2010;**15**:918–22.
72. Rave K, de la Peña A, Tibaldi FS, Zhang L, Silverman B, Hausmann M, et al. AIR inhaled insulin in subjects with chronic obstructive pulmonary disease: pharmacokinetics, glucodynamics, safety, and tolerability. *Diabetes Care* 2007; **30**:1777–82.
73. Kim HJ, Lee JY, Jung HS, Kim DK, Lee SM, Yim JJ, et al. The impact of insulin sensitisers on lung function in patients with chronic obstructive pulmonary disease and diabetes. *Int J Tuberc Lung Dis* 2010;**14**:362–7.
74. Lainscak M, von Haehling S, Doehner W, Sarc I, Jeric T, Ziherl K, et al. Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. *J Cachexia Sarcopenia Muscle* 2011;**2**:81–6.
75. Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol* 2003;**42**:1933–40.
76. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010;**11**:122.
77. Sarc I, Jeric T, Ziherl K, Suskovic S, Kosnik M, Anker SD, et al. Adherence to treatment guidelines and long-term survival in hospitalized patients with chronic obstructive pulmonary disease. *J Eval Clin Pract* 2011;**17**:737–43.