する際に，NADPH oxidaseが活性化されて産生されたROSが，インスリンシグナルを活性化させる．ROSの働きの1つに，インスリンシグナルであるチロシンキナーゼのリン酸化を不活化するプロテインフォスファターゼPTP1Bを不活性化状態にすることが知られている．PTP1BはGRXのレドックス制御によって活性化される．ホルモンや増殖因子の受容体やキナーゼと調節酵素フォスファターゼが，それぞれの活性部位近傍に存在するシステインのレドックスがGRXなどの酵素によって調節されていることで細胞の機能に重要な働きを及ぼしている．

肥満での脂肪細胞から産生されるTNFαがインスリン抵抗性に働くことが知られているが，最近，TNFαによってもたらされるインスリン抵抗性とTNFαによって産生されるROSとに深い関連があることが明らかとなってきた[6]．同じようにしてdexamethasone投与によるインスリン抵抗性出現にも機序は異なるものの，ROSが関与する．抗酸化物質の投与によってインスリン抵抗性が改善される可能性も示唆している．すなわち，生理的な状態で産生されるROSが関連するシグナル伝達を慢性の酸化ストレスを生じる状態では，過剰なROSがその機構を阻害すると考えられる．慢性疾患でのレドックス制御の意義はこれからの検討課題である．

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INTERNAL MEDICINE

□ SYMPOSIUM I □

1. COPD Pathogenesis from the Viewpoint of Risk Factors

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Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation in the lungs. Smoking is one of the amongst major risk factors for the development of COPD. Environmental pollution, age, and airway hyperreactivity are also the risk factors. The protease-antiprotease imbalance and the oxidant-antioxidant imbalance cause airway inflammation and destruction. The genes related to these balances may contribute to development of COPD pathology. Candidate gene-association studies and linkage analyses have been reported for COPD patients. The alpha-1 antitrypsin, glutathione S-transferase, microsomal epoxide hydrolase, and matrix metalloproteinase, are candidate genes. In acquired factors for COPD pathology, the adenoviral latent infection may enhance airway inflammation, leading to airflow obstruction. The current progress and future visions of genetic predisposition of COPD are discussed.

Key words: Smoking, protease-antiprotease imbalance, oxidant-antioxidant imbalance, Gene-Association Studies, adenoviral latent infection may

(DOI: 10.2169/internalmedicine.46.1775)

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation in the lungs. Although COPD was the 12th largest disease burden in the world in 1990, it is estimated that it will rise to be the fifth largest disease burden by 2020 (1-4). The most important risk factor for the development of COPD is smoking (Fig. 1). However, only 10-20% of chronic heavy smokers develop symptomatic COPD, which indicates that a difference in susceptibility to tobacco smoke injury must exist and may be related to genetic factors (Fig. 2). Candidate gene-association studies and linkage analyses have been reported for COPD patients. We summarized the evidence for the role of the candidate genes in the pathological processes associated with COPD. This review describes the genetic predisposition of COPD. The current progress and future visions of genetic predisposition of COPD are further addressed.

1) Background and Risk Factors of Development of COOD

Chronic tobacco smoking is the major risk factor for the development of COPD, but only a relatively small proportion of smokers actually develop airway obstruction. Although there is a dose-response relationship between FEV1 and the extent of cigarette smoking, smoking history accounts for only approximately 15% of the variation in lung function. That is why the genetic predisposition of COPD may exist in smokers. Although cigarette smoking is the most important risk factor for the development of COPD, allergic airway inflammation, long-standing asthma, air pollutants, and diesel exhaust particles may also cause irreversible airflow limitation such as COPD. Environmental pollution, age, and airway hyperreactivity are also the risk factors. Destruction of the lung parenchyma leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil (Fig. 1).

2) Candidate Gene-Association Studies for the Development of COPD

a) The genes related to the protease-antiprotease imbalances

There are two major hypotheses on the cause of COPD and emphysema, such as the protease-antiprotease hypothesis and the oxidant-antioxidant hypothesis (5, 6). It is well known that the Z alpha (1)—antitrypsin homozygote is predisposed to developing early onset basal, panacinar emphy-

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DOI: 10.2169/internalmedicine.46.1775

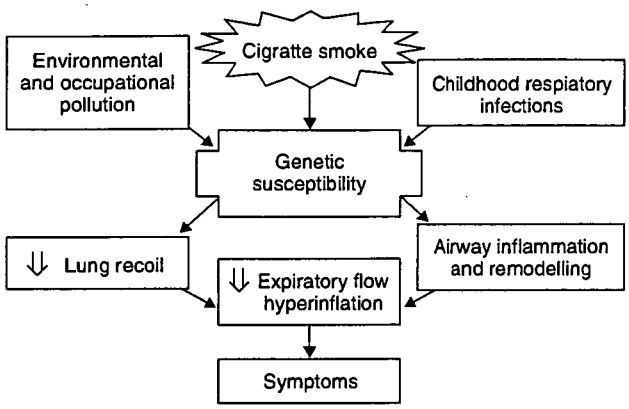
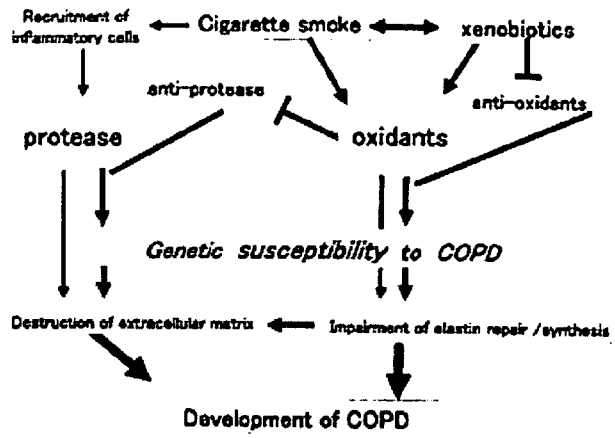


Figure 1. The risk factors for the development of COPD.



Teramoto S et al. Xenobiotic enzymes and genetics of COPD. Chest 2005 ; 127 : 408-409

Figure 2. Hypothesis of genetic susceptibility to COPD (6).

sema (7). In patients with the secretory defect of alpha (1)—antitrypsin, the lung tissue is under uncontrolled proteolytic attack from neutrophil elastase, culminating in alveolar destruction (8-12). The mouse metalloelastase knock-out studies implicate this enzyme as a key mediator in the pathology associated with cigarette smoke-induced emphysema (13, 14). There is also associative evidence from human genetic and animal studies suggesting a pathological link with other MMPs. The polymorphism of alpha-1-antichymotrypsin (AACT) and tissue inhibitor of metalloproteinases-2 (TIMP-2) gene polymorphisms may be associated with individual susceptibility to the development of COPD. The AACT/Ala-15 genotype may be less protective against smoking injury.

b) The genes related to the oxidant-antioxidant imbalance

Oxidative stress is believed to play an important role in the pathogenesis of smoking-induced COPD. The second hypothesis is the oxidant-antioxidant theory, which proposes that oxidant stress and reactive oxygen species (ROS), resulting from an oxidant/antioxidant imbalance, have important consequences for the pathogenesis of COPD. These include oxidative inactivation of antiproteinases, alveolar epithelial injury, increased sequestration of neutrophils in the pulmonary microvasculature, and gene expression of proinflammatory mediators. Several studies have provided supportive evidence of a role for reactive oxygen species (ROS) released from circulating neutrophils and the development of airflow limitation. Thus, the presence of oxidative stress may have important consequences for the pathogenesis of COPD. Number of studies have been done on the identification of genes that predispose to the development of COPD.

Heme oxygenase-1 (HO-1) plays a protective role as an antioxidant in the lung. The length of the (GT)n repeat in the 5'-flanking region of human HO-1 gene polymorphism is associated with susceptibility to COPD (15). The polymorphisms of antioxidant genes glutathione S-transferase M1 (GSTM1) and GSTP1 are reported to be associated with susceptibility to an accelerated decline of lung function in smokers (16, 17).

c) Xenobiotic enzymes and genetics of COPD

Each puff of a cigarette contains 10^{17} free radicals and about 4000 substrates including carcinogenic agents and other possible causative agents of COPD such as volatile aldehydes and hydrogen cyanide. Thus, defects in the detoxification of these reactive species may predispose smokers to airflow obstruction and emphysema. It has been suggested that genetic polymorphisms of cytochrome P450, microsomal epoxide hydrolase (mEPHX) are associated with emphysema or COPD (18-20). The genetic polymorphism of exon 5 of smokers with glutathione S-transferase P1 (GSTP 1) is associated with the development of COPD in smokers (3). There is growing evidence for the role of xenobiotics and antioxidant imbalance in the pathogenesis of airflow obstruction, which is supported by association studies between COPD and variants in epoxide hydrolase and GSTs that detoxify free radicals and other tobacco products (10-14).

d) Other genes associated with the genetic predisposition to COOD

Because airway obstruction is due to both loss of lung elastic recoil and inflammatory narrowing of peripheral airways, genetic polymorphisms that affect either process could be involved. It has been suggested that genetic polymorphisms of tumour necrosis factor-α, interleukin-13 (IL-13) gene promoter, and Vitamin D binding protein gene are associated with emphysema or COPD (21-23).

3) The Pathologic Relationship between Respiratory Illness in Childhood and Chronic Air-Flow Obstruction in Adulthood. —Adenoviral Latent Infection Thytpothesis—

It has been suggested that respiratory illness in childhood might cause chronic air-flow obstruction in adulthood. Hogg

DOI: 10.2169/internalmedicine.46.1775

JC and colleagues have suggested an association between latent adenoviral infection with expression of the adenoviral E 1A gene and COPD (24, 25). The present study focuses on how the adenoviral E1A gene could alter expression of growth factors by human bronchial epithelial (HBE) cells. The data show that connective tissue growth factor (CTGF) and transforming growth factor (TGF)-beta 1 mRNA and protein expression were upregulated in E1A-positive HBE cells. The latent infection of epithelial cells by adenovirus E 1A could contribute to airway remodeling in COPD by the viral E1A gene, inducing TGF-beta 1 and CTGF expression and shifting cells to a more mesenchymal phenotype.

Conclusion and Implication

Chronic obstructive pulmonary disease (COPD) is the collective term describing two separate chronic lung disease diseases: emphysema and chronic bronchitis. Results of many studies have suggested that the genetic susceptibility to COPD is dependent on the action of several gene polymorphisms operating in concert. Polymorphisms in an individual gene may impart only a small relative risk of COPD, and it is likely that the cumulative effect of many polymorphisms will be important in its pathogenesis. Before these associations are generally accepted, they must be subjected to scrutiny with further association studies in terms of ethnicity and COPD phenotypes.

Acknowledgements: This work was supported by a grant from Mitsui Life Social Welfare Foundation.

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EFFECTS OF AGE AND SEX ON PLASMA ADRENOMEDULLIN LEVELS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

To the Editor: It has been recognized that obstructive sleep apnea syndrome (OSAS) is one of the risk factors of cardiovascular disorders, including hypertension, ischemic heart disease, and cerebrovascular diseases.[1–3] Although the incidence of sleep apnea increases with age, the pathological roles of OSAS have not been fully established. OSAS-induced hypoxic stress and oxidative stress increase circulating inflammatory mediators, including adhesion molecules, inflammatory cytokines, and high-sensitivity C-reactive protein, leading to hypertension and cardiovascular events.[4,5] The stress and its related inflammatory molecules are implicated in the production of adrenomedullin (AM), which is a potent endothelial-derived vasodilator.[6] Circulating AM levels are higher in adults with untreated OSAS than in adults without OSAS.[7] Because plasma AM is closely correlated with pulse wave velocity and atherosclerosis progression in middle-aged and elderly patients, higher levels of AM may be a surrogate marker for hypertension and the progression of atherosclerosis.[8] Furthermore, treatment with nasal continuous positive airway pressure (nCPAP) mostly reversed the higher AM levels in subjects with OSAS. Thus, OSAS treatment may prevent atherosclerosis and cardiovascular events, although circulating AM levels and therapeutic response to OSAS have not been examined in elderly people. Furthermore, female sex hormones increase AM-induced vasodilation by increasing the expression of AM2 receptor components in rats.[9] Sex may affect circulating AM levels in humans.

Age and sex differences in AM levels in patients with OSAS were examined. Eighty middle-aged (aged 40–60) and 80 elderly (aged 60) patients were compared with OSAS and 80 middle-aged and 80 elderly age- and body mass index (BMI)-matched subjects without OSAS. The patients had to fulfill the following criteria: absence of renal and renovascular hypertension, systolic blood pressure (BP) greater than 160 mmHg or diastolic BP greater than 95 mmHg, chronic renal and hepatic diseases, and diabetes mellitus. Patients who smoked or had systemic infections at the time of the study or within 4 weeks before the study were excluded. No patients were being treated with antihypertensive agents. These subjects were examined using polysomnography; subjects with an apnea-hypopnea index (AHI) less than five were controls, and those with an AHI of five or greater were determined to have OSAS. To assess OSAS-induced hypoxia quantitatively, the oxyhemoglobin desaturation index (ODI) was used in this study as previously described.[4] ODI was defined as $ODI = \Sigma(90 - \text{oxygen saturation})t$, where t is time of desaturation (hours).[4]

Circulating AM levels and sleep study variables were compared. Then 3 months of nCPAP treatment was performed in the patients. Peripheral blood was obtained from the subjects at 7:30 a.m. to 8:00 a.m. before and after the 3 months treatment with nCPAP. The AM was measured using a specific radioimmunoassay.

There were no significant differences in BMI between the patients and controls in each age group, whereas AHI in subjects OSAS was markedly greater than in controls (Table 1). There were no significant differences in BP or metabolic indices. The AHI values in elderly (50.1 ± 3.2 events/h) and middle-aged (51.6 ± 3.0) subjects with OSAS were considerably greater than in age-matched controls (3.8 ± 0.3 and 3.6 ± 0.4, respectively). There were significant differences in baseline ODI between patients with OSAS and controls, suggesting that the patients with OSAS were exposed to a

Table 1. Circulating Adrenomedullin (AM) Levels and Other Variables in Elderly and Middle-Aged Patients with Obstructive Sleep Apnea Syndrome (OSAS) and Controls

Characteristic	Middle-Aged Subjects with OSAS (n = 80)	Elderly Subjects with OSAS (n = 80)	Middle-Aged Controls (n = 80)	Elderly Controls (n = 80)
	Mean ± Standard Error			
Age	46.8 ± 2.2	65.8 ± 2.2	45.1 ± 2.2	64.8 ± 2.1
Body mass index	33.4 ± 0.9	32.1 ± 0.9	32.8 ± 1.1	31.5 ± 1.1
Systolic blood pressure, mmHg	138.1 ± 3.7	139.1 ± 4.7	135.6 ± 4.1	137.1 ± 3.7
Diastolic blood pressure, mmHg	82.1 ± 3.2	80.1 ± 3.2	78.9 ± 3.8	78.1 ± 2.8
Total cholesterol, mg/dL	202.9 ± 7.9	199.1 ± 6.9	202.9 ± 7.9	198.3 ± 10.8
High-density lipoprotein cholesterol, mg/dL	43.0 ± 2.2	41.0 ± 2.1	43.6 ± 2.3	42.2 ± 2.1
Triglyceride, mg/dL	144.1 ± 10.7	137.1 ± 12.7	140.1 ± 10.7	132.0 ± 10.9
Fasting plasma glucose, mg/dL	98.4 ± 1.3	94.6 ± 1.3	97.6 ± 1.4	90.3 ± 1.1
Hemoglobin A1c, %	5.7 ± 0.1	5.8 ± 0.1	5.6 ± 0.1	5.27 ± 0.1
Total sleep time, min	368.1 ± 20.3*	348.1 ± 20.3*	440.3 ± 20.9	414.3 ± 20.9
Apnea–hypopnea index, events/h	51.6 ± 3.0*	50.1 ± 3.2*	3.8 ± 0.3	3.6 ± 0.4
Lowest oxygen saturation, %	67.2 ± 2.1*	68.9 ± 3.0*	95.8 ± 0.5	94.1 ± 0.5
Oxyhemoglobin desaturation index	2.45 ± 0.32*	2.41 ± 0.36*	0.02 ± 0.01	0.02 ± 0.01
Arousal index,/h	42.4 ± 3.1*	40.2 ± 2.2*	8.3 ± 3.1	8.3 ± 3.1
AM level, pg/mL	49.1 ± 3.7	51.1 ± 4.1*	24.8 ± 1.9	25.7 ± 2.1

Note: There were 40 men and 40 women in each group.
*$P < .001$ versus control group.

significantly greater degree of hypoxia than the control subjects. The magnitude of ODI was not different between middle-aged and elderly patients with OSAS.

Circulating AM levels in middle-aged and elderly patients with OSAS were significantly greater than in the age- and BMI-matched controls, although neither age nor sex affected them (Table 1). nCPAP treatment significantly decreased the higher levels of circulating AM in the patients irrespective of age and sex. After 3 months of treatment with nCPAP, AM levels in elderly patients (26.5 ± 2.4 pg/mL) were not different from those of middle-aged patients (24.7 ± 2.1 pg/mL).

These results indicated that plasma AM levels were higher in middle-aged and elderly patients with OSAS and could be deceased with nCPAP treatment, regardless of age and sex. The augmented increase in AM caused by severe nocturnal hypoxemia and oxidative stress due to OSA may overcome the age-dependent increase of AM levels in middle-aged and elderly patients with OSAS. Because AM is reported to induce cell surface expression of adhesion molecules, including E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 (ICAM-1), on human endothelial cells, the higher level of AM is one of the mechanisms of higher levels of ICAM-1 in patients with OSAS.[10] The current study also indicates that treatment with nCPAP may be effective for the prevention of cardiovascular complications in elderly patients with OSAS.

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ACKNOWLEDGMENTS

This work was supported in part by a research grant from Mitsui Life Social Welfare Foundation Japan fund and by research grant from Mitsukoshi Health and Welfare Foundation in Japan. There is no conflict of interest regarding the study.

Conflict of Interest: The editor in chief has determined that the authors have no conflict of interest regarding this study.

Author Contributions: study concept and design, Shinji Teramoto, MD, Yasuhiro Yamaguchi; acquisition of subjects and/or data analysis, Hiroshi Yamamoto, MD, Yoko Hanaoka, MD, Masaki Ishii, MD, Shinichiro Hibi, MD; interpretation of data, Haruki Kume, MD, Masahiro Akishita, MD; preparation of manuscript, Yasuyoshi Ouchi, MD.

Sponsor's Role: No sponsor in this study.

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NATURAL THERAPIES—WHEN IGNORANCE IS NOT BLISS!!

To the Editor: A 72-year-old Caucasian man with history of hypertension, dyslipidemia, depression, gastroesophageal reflux disease, and mild obesity presented to the hospital with intractable singultus (hiccups) for approximately 9 days, associated with anorexia and epigastric pain. He had presented to his primary care provider the day before admission and was given prochlorperazine without relief. His daily medications were metoprolol, furosemide, fluvastatin, gemfibrozil, paroxetine, and omeprazole. A thorough history revealed that he had added 2 tablespoons daily of acetic acid (household vinegar) to his routine for the previous 2 weeks after reading an article in a health magazine that indicated that vinegar helps decrease food intake (by promoting satiety) and lowers cholesterol. Physical examination was unremarkable except for mild epigastric tenderness.

Computerized tomography of the abdomen with oral and intravenous contrast was suggestive of acute pancreatitis, and amylase and lipase levels were elevated, at 876 and 1,187 U/L, respectively. Other laboratory parameters were normal. Brain imaging and endoscopy were negative, and furosemide and paroxetine were discontinued on admission. The patient received nothing by mouth and was maintained with intravenous fluids for 2 days. He experienced complete resolution of the pancreatitis and the hiccups.

Vinegar has a long history in medicine, including use by the father of modern medicine, Hippocrates, as an agent to fight acute infections and chronic coughs. Some modern studies support antimicrobial effects with food preparation; others claim it is a nematocyst inhibitor and protective in stings by some jellyfish. Recently, vinegar has been identified as an antiglycemic in subjects with and without glucose intolerance. In addition, it has been shown to increase satiety in healthy patients.[1]

There have been various adverse effects of vinegar described in the literature. Some of these include corrosive

It is not correct to say that "a quarter of centres did not measure height". We reported that: "Out of 42 centres, it was measured in 31, self-reported in five and not recorded whether measured or asked in six." We were being scrupulously honest and in five of the latter it is likely that height was measured. However, study personnel have moved on and definitive information could not be retrieved once we had realised that some centres had not measured height directly. In three of the centres that we classed as "self-reported height", subjects were measured if any doubt was expressed, and gross errors are unlikely to have occurred. Although the over-estimation of height in the study by STEWART *et al.* [3] was nontrivial, that found by NIEDHAMMER *et al.* [4] was <0.5 cm on average. The other reference does not seem relevant.

There was exclusion for non-White ethnicity in only one centre: Melbourne (Australia). Ethnicity was not recorded in any of the other centres, which are listed in table 1 of our paper [1], but this was not raised as an issue.

It was our intention in writing the paper to engender debate and our conclusions are endorsed by S. Stanojevic and co-workers. We believe that current reference curves cannot be guaranteed to give accurate norms of lung health, and that multicentre studies must invest substantially in standardised equipment. However, "statistical models which can adjust for between-centre differences", as advocated by S. Stanojevic and co-workers, do not solve the problem, as differences may be due to genuine variation in health.

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DOI: 10.1183/09031936.00125506

Improvement of endothelial function with allopurinol may occur in selected patients with OSA: effect of age and sex

To the Editors:

In a recent issue of the *European Respiratory Journal*, EL SOLH *et al.* [1] demonstrated that allopurinol improves endothelial dysfunction in patients with moderate-to-severe obstructive sleep apnoea (OSA). Because xanthine oxidase inhibition with allopurinol prevents the formation of superoxide free radicals, which leads to better endothelial function, EL SOLH *et al.* [1] speculated that excess activity of xanthine oxidase contributes significantly to vasodilatory impairment in patients with OSA.

The study was a sophisticated prospective, randomised, crossover design, minimising the presence of confounding variables and eliminating inherent individual variations in terms of the generation of free radicals, hyperaemic vascular reactivity or response to treatment. However, a number of arguable assumptions were made in the article of EL SOLH *et al.* [1].

First, endothelial function assessment using hyperaemia-induced flow-mediated vasodilation (FMD) is not always suitable for the assessment of endotheloial function in female obese patients with sleep apnoea. There is a significant relationship between FMD and brachial artery size; therefore, as males have larger arterial diameters, smaller FMD is noted in males [2]. Thus, the changes in FMD in males before and after therapeutic intervention are usually larger than those in females. As the current study did not examine the FMD results of females and males separately, the sex difference may exist in the study. Inversely, the FMD improvement after allopurinol treatment may be clearly indicated, when the males' results were analysed separately from the females' results.

Secondly, FMD of the brachial artery diminished with age [2]. Thus, the age distribution of the study sample affects the results of the FMD alterations after intervention. Because the authors examined subjects aged 29–60 yrs, this wide range of the population may not represent the genuine effects of allopirinol on the FMD in association with oxidative stress due to sleep apnoea itself.

Thirdly, obesity without sleep apnoea also causes endothelial dysfunction [3]. The FMD results should be standardised by the body mass index (BMI) or metabolic variables, when the FMD results are properly assessed. In the study by EL SOLH *et al.* [1], BMI ranged 23–67. We speculate that the FMD results in patients with a normal BMI of 24 might be very different from the extraordinarily obese patients with a BMI of 67. It has also been reported that FMD is associated with systemic inflammation and glucose homeostasis in obese patients, independent of

obesity [4]. Because both obesity and sleep apnoea cause systemic inflammation [5, 6], the association of the inflammatory markers and insulin sensitivity with FMD should be further examined.

Fourthly, the menopause and menstrual cycle significantly affect sleep apnoea and endothelial function [7, 8]. The menopausal transition is significantly associated with an increased likelihood of having sleep-disordered breathing, independent of known confounding factors [7]. FMD increases in menstrual phase, when serum oestradiol level is low and the value is comparable to that in male subjects [8]. Because endothelium-dependent vasodilatation varies during the menstrual cycle, the timing of FMD measurements of female subjects is critical for the precise assessment of allopinol effects.

The incidence of cardiovascular disease is lower in premenopausal females compared with males in the same age group; following menopause, the risk of mortality from cardiovascular disease increases in females [9]. FMD-induced vasodilatation is lower in females aged 55 yrs than those aged 35 yrs [10]. The lower FMD in females aged 55 yrs, compared with those aged 35 yrs, could be due to postmenopausal hormonal changes.

It has been suggested that endothelial function assessment using hyperaemia-induced FMD is adequately reproducible in healthy middle-aged males and females [2]. However, there are many confounding factors including age, sex, obesity, smoking, elevated blood lipids, high blood pressure and systemic inflammation. Thus, FMD measurement may not be an appropriate method for the assessment of the endothelial function in female obese patients with sleep apnoea.

Further study using a large sample size should be carefully assessed by age, obesity and sex differences. The improvement of endothelial function by allopurinol effects on the vascular function in patients with sleep apnoea will then be adequately realised.

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DOI: 10.1183/09031936.00104806

From the authors:

We thank S. Teramoto and colleagues for their comments on our recent article [1]. We agree that changes in flow-mediated vasodilation (FMD) are influenced by a variety of intrinsic and extrinsic factors such as endogenous, environmental and familial factors [2], of which age, sex and body mass index (BMI) are the classic examples. Indeed, analysis by sex of our data showed that male participants had larger arterial diameters and smaller FMD at baseline compared with female subjects ($6.1 \pm 2.6\%$ in males and $8.0 \pm 1.7\%$ in females). However, in contrast to the remarks of S. Teramoto and colleagues, the median FMD improvement after allopurinol treatment was larger in women (4.3%; 95% confidence interval (CI) 1.0–7.6%) than in their male counterparts (3.4%; 95% CI 1.5–5.4%); although not to a statistically significant degree. Correlation analyses also revealed no significant relationship between changes in FMD (before and after treatment) and either age ($r=0.2$; $p=0.5$) or BMI ($r=0.06$; $p=0.85$). We acknowledge that the power of the study is too small to detect any significant difference and we alluded to this limitation in the manuscript. As pointed out by S. Teramoto and colleagues, FMD is influenced by circulating levels of oestrogen and progesterone, and by the phase of the subject's menstrual cycle [3]. This variability would have been significant had our female participants been of a child-bearing age; however, only one of the four female subjects fell into that category. Finally, we concur with S. Teramoto and colleagues that a larger sample size would be needed to confirm our findings. Now that our randomised clinical trial has shown potential efficacy, we hope it stimulates further long-term research studies to determine the role and side-effects of allopurinol in the treatment of obstructive sleep apnoea-related endothelial dysfunction.

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DOI: 10.1183/09031936.00111906

ACE inhibitors prevent aspiration pneumonia in Asian, but not Caucasian, elderly patients with stroke

To the Editors:

In a recent issue of the *European Respiratory Journal*, VAN DE GARDE *et al.* [1] demonstrated that the use of angiotensin-converting enzyme (ACE) inhibitors is not associated with a decreased risk of hospitalisation for community-acquired pneumonia (CAP) in a general, essentially white population. Their conclusion that the beneficial effect of ACE inhibitors on pneumonia risk is not observed in a general white population is in contrast with previous findings in Asian populations [1]. This was an excellent good study examining the association of ACE inhibitor treatment of cardiovascular disease with a risk reduction of CAP using a large sample size. The results are acceptable and not surprising; however, the discussion and conclusion are misleading.

As shown in table 1, there are controversies regarding the ACE inhibitor effects on the risk reduction of pneumonia even in Asian countries; furthermore, the study samples are very different among the studies. In a prospective study by SEKIZAWA *et al.* [2], ACE inhibitor use reduced pneumonia incidence for 2 yrs. They did not examine the general population; subjects were hypertensive elderly patients with a history of stroke or lacuna infarction, and a mean age 10 yrs older than that of the study by VAN DE GARDE *et al.* [1]. However, the study by ARAI *et al.* [3] examined the association of ACE inhibitors and the risk reduction of pneumonia in the general hypertensive elderly without stroke in Japan [3]. Surprisingly, they had an 8.3–8.9% incidence of pneumonia over 3 yrs, an incidence twenty times higher than the previous data [6, 7]. It is hard to believe that ~3% of hypertensive elderly outpatients without major complications suffered from pneumonia. We have previously presented data showing no association of ACE inhibitor use with pneumonia risk in elderly hypertensive subjects without stroke history [4]. Since ACE inhibitors, through the inactivation substance P, improve upper airway reflexes such as swallowing and cough, resulting in the reduction of aspiration pneumonia in elderly patients, they may not reduce the CAP in those patients without deglutition problems. Current evidence indicates that ACE inhibitors play a significant role in the prevention of aspiration pneumonia in the elderly, but not in common CAP in healthy adults. This was confirmed by the sub-analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). OHKUBO *et al.* [5] re-analysed the PROGRESS data concerning the incidence of pneumonia. ACE inhibitor-active treatment significantly reduced the risk of pneumonia among participants of Asian ethnicity (mean (95% confidence interval) 47% (14–67%), p=0.01), with no significant effect among non-Asian participants (5% (-27–29%), p=0.7; p for homogeneity=0.04). These findings add to the body of

TABLE 1 The association of angiotensin-converting enzyme (ACE) inhibitor use and the rate of pneumonia in different trials

	VAN DE GARDE [1]	SEKIZAWA [2]	ARAI [3]	TERAMOTO [4]	OHKUBO [5]	OHKUBO [5]
Race	Caucasian	Asian	Asian	Asian	Asian	Caucasian
Age yrs	67	76–77	75.3–76.5	>65	64	64
Subjects n	4925	440	576	358	2352	3753
Observation period yrs	6	2	3	3	3.9	3.9
History of stroke	No	Yes	No	No	Yes	Yes
Pneumonia incidence %						
Without ACE inhibitors		9	2.77–2.97	0.25	1.04	1.3
With ACE inhibitors		3.5	1.1	0.56	0.56	1.24
Pneumonia prevention by ACE inhibitors	No	Yes	Yes	No	Yes	No

evidence regarding the effects of these drugs on pneumonia. The randomised design of PROGRESS greatly reduced the likelihood of confounding of the analyses and provided an excellent opportunity to explore the validity of the associations reported in observational studies [2, 3]. Thus, the key issue is the selection of elderly subjects in terms of ethnicity, post-stroke state, performance status, type of ACE inhibitor and swallowing function.

The clinical epidemiology research group of ETMINAN *et al.* [8] recently reported that no association was found between the use of ACE inhibitors or angiotensin II receptor blockers (ARBs) and risk of hospitalisation secondary to CAP. The study further confirmed the limited efficacy of ACE inhibitors on the risk reduction of hospitalisation due to pneumonia in a white population. As we speculated, ARBs did not have any role in the prevention of aspiration pneumonia.

Stroke and post-stroke patients often exhibit a normal cough reflex, but not swallowing reflex, and the small volume of aspirated materials due to impaired swallowing during night is a key factor for the risk of pneumonia [9, 10]. Hence, a ten times higher rate of pneumonia in post-stroke patients without significant neurological deficit, compared with the rate of pneumonia in normal elderly [5]. Furthermore, the age-dependent impairment of upper airway reflexes should be carefully considered for the mechanism of CAP in the elderly irrespective of the history of stroke.

Finally, we emphasise that aspiration and silent aspiration are very important mechanisms of aspiration pneumonia. Silent aspiration is very common in patients with stroke and frail elderly patients, and nasogastric tube feeding without swallowing rehabilitation or oral care cannot reduce the pneumonia risk in patients with swallowing disorders [11].

We believe that angiotensin-converting enzyme inhibitors could prevent aspiration pneumonia in selected elderly patients. Post-stroke and the frail elderly are the best candidates for the pneumonia risk reduction by angiotensin-converting enzyme inhibitors [12]. However, these merits may not be consistently observed in Caucasian elderly patients with or without stroke.

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DOI: 10.1183/09031936.00115106

From the authors:

I would like to thank S. Teramoto and co-workers for their response to the study my co-workers and I performed on the effects of angiotensin-converting enzyme (ACE) inhibitors on the risk of acquiring pneumonia. Indeed, we could not confirm an association between the use of ACE inhibitors and the risk of pneumonia in a general population. This, however, does not exclude any beneficial effects of ACE inhibitors in specified patient subgroups.

As mentioned in our introduction and by S. Teramoto and co-workers, it is known that patients with a history of stroke do have a higher risk of acquiring pneumonia, which is particularly due to a reduced cough and swallowing reflex [1, 2]. That ACE inhibitors can be beneficial in these patients is already widely reported [3–5]. We aimed to study whether this protective effect can also be extended to the general population. Unfortunately, we were not able to test modification of the association through stroke, as data on stroke history were sparsely available in the database.

Concerning ethnicity, the reason why the association could not be confirmed in the non-Asian participants of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) is still subject to speculation. Genetic differences should certainly be considered. However, OHKUBO *et al.* [4] were unable to show an influence of the ACE I/D polymorphism on the protective

that these changes became more convincing with time, so that a longer term study with higher doses is rational. Finally, the measurement of cytokines, such as TNF-α, in induced sputum might be a useful way to select those patients who may respond to therapy directed against TNF-α, and could have utility in monitoring therapeutic responses.

Conflict of Interest Statement: E.M.E. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. O.M.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.J.B. has received funding and has served on scientific advisory boards for GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim, Novartis, Altana, Pfizer, and Millennium. T.T.H. has received research grants in 2004 to May 2006 from GlaxoSmithKline ($250,000), Novartis ($500,000), and Oxogen ($360,000).

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Aging, the Aging Lung, and Senile Emphysema Are Different

To the Editor:

In his recent editorial, Tuder implicated the pathophysiologic interrelationship between aging and cigarette smoke in the development of chronic obstructive pulmonary disease (COPD) (1). We believe that some of the points in this editorial are misleading.

First, aging is a process leading to death and is characterized by universal progressive, deleterious, and irreversible alterations. But aging is not a disease. We can treat the age-related phenomena, but not aging itself. Tuder is commenting on the article by Sato and coworkers in the same issue, which is entitled "Senescence Marker Protein-30 Protects Mice Lungs from Oxidative Stress, Aging, and Smoking" (2). Sato and coworkers' title is incorrect. Importantly, previous studies have described physiologic changes of the lungs due to aging alone as aging lung or senile lung, but not as senile emphysema (3, 4). Here, the lungs were characterized as undergoing airspace enlargement without alveolar wall destruction (3, 4). Also, Janssens and coworkers' review, which was cited by Tuder, did not correctly differentiate the difference between aging lung and senile emphysema (5). Thus, age itself is known to be a risk for COPD, but not necessary for the development of COPD.

Second, gene regulation of aging is complex. The master gene of aging has not been determined, although the Klotho gene is a candidate (6). Klotho gene–deficient mice develop the airspace enlargement without cigarette smoke exposure. Although mouse models of COPD often exhibited homogeneous alterations of lung structures, age-related changes of the lungs are heterogeneous in humans. The role of a single gene on the functional and morphologic changes of the lungs may be limited in humans. The redundancy of multiple genes associated with aging may substitute for the impaired cell function of lungs in humans due to a single gene defect.

Third, there is no association of apoptosis and aging in human lungs. In particular, apoptotic cell death is not directly related to the aging process. Because apoptosis is an active process, it is not related to a degenerative process such as aging.

We realized that the senescence marker protein-30 (SMP-30) gene is a good candidate gene for exploring the aging process and age-related diseases. However, the pathologic interaction between the aging process and COPD may not be solved by analyzing the SMP-30 gene and its protein products. We should differentiate physiologic aging, such as the aging/senile lung, from pathologic aging, as in senile emphysema (4). Furthermore, the resemblances and differences between senile emphysema and adult COPD should be better clarified.

Conflict of Interest Statement: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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From the Author:

My editorial's intent was to highlight the cellular and molecular events that mechanistically link aging and chronic obstructive pulmonary disease (COPD), and to stimulate further research on this important topic (1). Such studies may help resolve the controversies raised by Drs. Teramoto and Ishii regarding the definition of aging, whether aging should be interpreted as a physiologic or pathologic process, and the relationship between lung alterations due to aging vis-à-vis senile emphysema. It is apparent that the concept of a so-called physiologic lung aging, as argued by Drs. Teramoto and Ishii, deserves careful revaluation. Significant pathologic processes are evident with the onset of aging, such as excessive oxidative stress, DNA damage, enhanced inflammation, and decreased immunity, all of which might contribute to a significantly higher incidence of cancer and degenerative diseases compromising the heart (with heart failure), muscle (with muscle wasting), and joints (with osteoporosis), among others (2).

Why should the lung be different from the heart, brain, or immune system? It is conceivable that age-related molecular and cellular injuries may be of significant pathophysiologic importance in the causation of many pulmonary diseases, including COPD or lung cancer. Indeed, prior work by Dr. Teramoto acknowledges the close resemblance of lung alterations due to aging to those related to environmental injuries (including cigarette smoke inhalation). He raises similar considerations regarding the effect of age on cigarette smoke–induced emphysema to those posed in my editorial and the accompanying article by Sato and coworkers (3).

Aging alters fundamental controls involved in cell growth, maintenance, and death. Accumulation of stresses over the life span shortens telomeres, a hallmark of senescent cells (4). Telomere shortening was recently recognized to be present in COPD lungs in association with increased expression of Ink4a/Arf (5), a biomarker of aging (6). These advances and the recognition of alveolar cell apoptosis, oxidative stress, and senescence have been linked to emphysematous lung destruction (5, 7), warranting the revaluation of prior definitions of alveolar enlargement in both diseased (i.e., COPD) and aging lung (8). Transgenic mice provide important and useful tools for exploring how candidate genes, such as SMP-30 and the Klotho protein, trigger pathogenetic mechanisms involved in destructive alveolar enlargement. These studies will enrich the list of candidate genes potentially involved in aging and in COPD in humans. In addition, these discoveries will further clarify how COPD risk factors, including sex, childhood diseases, cigarette pack-years, and infections might also enhance the susceptibility to the disease.

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Conflict of Interest Statement: R.M.T. has received $2,500 for a lecture given in a meeting on COPD sponsored and organized by AstraZeneca. He has received an unrestricted gift of $100,000 from Quark Biotech to conduct research in the pathogenesis of emphysema, particularly of the pathway involving RTP-801.

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Should Individuals Who Are Tuberculin Skin Test Negative and Positive to RD1–IFN-γ Assay Receive Preventive Therapy?

To the Editor:

We read with interest the recent pulmonary perspective by Luca Richeldi about the use of blood tests for the diagnosis of tuberculosis infection (1). Richeldi reviews the evidence suggesting that tests based on *in vitro* release of IFN-γ in response to *Mycobacterium tuberculosis* region of difference 1 (RD1)-antigens, in particular those based on the enzyme-linked immunospot (ELISpot) technique, may be more sensitive than the tuberculin skin test (TST) for the diagnosis of tuberculosis infection. He also argues that routine use of these tests may result in short-term increased costs due to more diagnosis of and treatment for tuberculosis infection. In our opinion, if the preliminary evidence on ELISpot sensitivity is confirmed, other issues, besides that of costs, need also to be addressed before replacing TST in screening programs for latent tuberculosis with more sensitive blood tests.

Lord and coworkers recently analyzed the level of evidence needed to accept a new diagnostic test in routine practice (2). These authors argue that when a new test is more sensitive than an old one, the extra cases detected by the new test may represent a different spectrum of disease compared with those detected by the old test. Thus, the information about the effect of treatment of cases diagnosed by the old test may not necessarily apply to extra cases detected by the new test. The recent paper by Ewer and coworkers (3) suggests that new blood tests for tuberculosis infection may indeed produce a shift in the spectrum of infection detected. These authors identified 14 students who were TST-negative and ELISpot-positive among contacts in a school tuberculosis outbreak. None of them received preventive therapy, and seven became ELISpot-negative during follow-up. In contrast, no change in ELISpot response was observed in the ELISpot-positive, but untreated TST-positive staff. The authors suggested that individuals who were ELISpot-positive only may have been infected with a lower dose of *M. tuberculosis*, insufficient to induce a cutaneous response to PPD.

Available data on the benefit of treatment of latent tuberculosis infection are based on trials using TST-positive individuals (4). It remains to be demonstrated that a similar benefit could be found in TST-negative individuals who are positive to IFN-γ

The great jurist Oliver Wendell Holmes (1841–1935) stated: "I would not give a fig for simplicity this side of complexity, but I would give my life for simplicity on the other side of complexity." As geriatricians, we have understandably become aficionados of late-life complexity, although if it is our goal one day to have a truly transformational effect on the major causes of disability in our frail patients, we too must look for hints of simplicity beyond complexity. In this context, we agree with Drs. Rockwood and Mitnitski that an A or A+ grade for our field is premature and should await our or our successors' ability to accomplish the second half of Oliver Wendell Holmes' most insightful statement.

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ACKNOWLEDGMENTS

Conflict of Interest: This work was presented in part as a Symposium at the American Geriatrics Society 2006 Annual Scientific Meeting. The authors would like to thank the AGS Research Committee for sponsorship of this symposium. Dr. Inouye is supported in part by Grants K24AG00949 and R21AG025193 from the National Institute on Aging and by the Milton and Shirley F. Levy Family Chair. Dr. Studenski is supported in part by National Institutes of Health Grant K07AG023641 and Pittsburgh Older Americans Independence Center (OAIC) Grant P30AG024827. Dr. Tinetti is supported in part by a grant from the Patrick and Catherine Weldon Donaghue Medical Research Foundation, by the Yale OAIC (P30AG021342), and by the Gladys Phillips Crofoot Chair. Dr. Kuchel was supported in part by grants from the National Institute on Aging (R01AG028657) and the Patrick and Catherine Weldon Donaghue Medical Research Foundation, as well as the Travelers Chair in Geriatrics and Gerontology. Dr. Stephanie Studenski has served as a consultant for Merck and Amgen and has had an unrelated research project funded by Eli Lilly and Co. Dr. George Kuchel has served as a consultant for Johnson and Johnson, Pfizer, and Odyssey Pharmaceuticals.

Author Contributions: Preparation of the letter (GAK), critical review and approval (all authors).

Sponsors' Role: None.

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SMALL INTESTINAL INTUSSUSCEPTIONS CAUSED BY PERCUTANEOUS ENDOSCOPIC JEJUNOSTOMY TUBE PLACEMENT

To the Editor: With the extraordinary increase in the elderly population, artificial enteral nutrition arises as a major concern in geriatric medicine and home care. The placement of a percutaneous endoscopic gastrostomy (PEG) tube is a safe and widely accepted method of artificial enteral nutrition in frail elderly people, although the presence of hiatus hernia, severe reflux esophagitis, and frailty are predictive factors for aspiration or vomiting after PEG tube placement.[1]

In patients at risk of severe gastroesophageal reflux (GER), percutaneous endoscopic jejunostomy (PEJ) is an alternative approach to safe enteral feeding,[2] although a risk of tube-related problems accompanies PEJ tube placement.[3] Here we report an unusual case of small intestinal intussusceptions caused by PEJ tube placement.

A 94-year-old woman was repeatedly admitted to the University of Tokyo hospital for aspiration pneumonia and lung inflammation caused by pulmonary nontuberculous mycobacterium infection.

Because of her bedridden condition and complaints of severe dysphagia, malnutrition, and hiatus hernia, PEJ was performed instead of PEG for enteral feeding. The PEJ tube was changed every 2 months without complications. Six months after the initial PEJ tube placement, she developed aspiration pneumonia again and was readmitted to the hospital. Although the lung inflammation exhibited steady improvement with antibiotic administration, she had occasional episodes of diarrhea, vomiting, and lower abdominal

Figure 1. Abdominal computed tomography showing the small intestinal intussusceptions 8 inches in length and along the axis of the percutaneous endoscopic jejunostomy tube. The distended 3-inch-long jejunal loop was located distal to the intussusceptions.

pain. Physical examination of her abdomen was unremarkable, and laboratory tests revealed a low-grade systemic inflammation, but abdominal computed tomography scans and radiographs obtained after infusion of a contrast medium into the PEJ tube revealed small intestinal intussusceptions associated with the PEJ tube (Figures 1 and 2). Because the small intestine was not completely obstructed, the patient was treated with intravenous therapy and drainage using ileus tubing. Her bowel function was normal within days, and she was subsequently transferred to another hospital.

Recently, PEJ has been considered to be a better method than PEG for preventing aspiration pneumonia, because the PEJ tube is inserted at a more distal intestinal area than the PEG tube.[2,4] However, the smaller size of the PEJ tube than the PEG tube may limit infusion speed and nutrient concentration. Tube dysfunctions rarely occur with PEJ tube placement; the present case is the first case of PEJ-induced small intestinal intussusceptions.[3] The cause of these intussusceptions could be the telescoping phenomenon and pleating of the proximal small bowel.[5] Adhesions may cause the fixing of these pleats, and the fixed pleats are considered the lead point for intussusceptions. Because bowel movement decreases with advancing age, a rare complication such as intussusception should be carefully considered after the induction of enteral feeding with PEJ.

Figure 2. Infusion of a contrast medium into the feeding tube revealed reduced diameter of the intestine distal to the intussusceptions.

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ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the checklist of financial and personal conflicts and has determined that there are no conflicts of interest with any of the authors on this paper.

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Sponsor's Role: None.

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SUBUNGUAL MELANOMA: A PARTICULARLY INVASIVE "ONYCHOMYCOSIS"

To the Editor: A 74-year-old woman was referred to our outpatient department for a serious nail dystrophy of her first left toe. She reported that an alteration of the nail pigmentation had appeared approximately 2 years before and that, at first, she had not given much importance to this modification. The lesion was neither painful nor symptomatic. Only after several months did she decide to go to her general practitioner for the progressive change of the nail plate.

Her physician diagnosed an onychomycosis and treated it with a specific topical remedy. The nail dystrophy went on

patients received full resuscitation; even in the 22% who were classified as receiving limitation of care, 18.8% were actually transferred out of the intensive care unit (ICU) terminally (left against medical advice) for financial or other reasons. Only 1.6% of ICU deaths had do-not-resuscitate orders and another 1.6% had withholding of life support [2]. A second study carried out at four centres in Mumbai [3] revealed that 34% of deaths had limitation of therapy terminally. Approximately 25% of these patients were not intubated terminally; 67% were initially intubated and ventilated but failed to recover and, subsequently, had no further escalation of therapy; and 8% had withdrawal of therapy [3].

Secondly, apart from the educational, social and cultural differences, the healthcare system in India differs substantially from that in Europe. In Europe, government and national health insurance account for 70% of total health expenditure [4] compared with 20% in India, where 80% of the total healthcare bill is paid by the patient or their relatives [5].

Thirdly, the ethical and legal status of withholding and withdrawal of life-sustaining therapy from critically ill patients in India is ambiguous. Concepts like autonomy and death with dignity have not been explored in any meaningful way by the constitution. Euthanasia and physician-assisted suicide are not legal. Consequently, physicians are often reluctant to pro-actively limit therapy.

Fourthly, India has less than one hospital bed per 1,000 people and an even lower number of ICU beds [5].

Given the scarcity of resources and growing needs in India, it is the right time for physicians and allied healthcare societies to educate the government and public about the magnitude of the problem, and to start a healthy dialogue in order to reach a constitutional and legal directive with regard to withholding and withdrawal of care in critically ill patients.

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STATEMENT OF INTEREST
None declared.

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DOI: 10.1183/09031936.00085707

Cardiovascular and metabolic effects of CPAP in obese obstructive sleep apnoea patients

To the Editors:

In a recent issue of the *European Respiratory Journal*, COUGHLIN *et al.* [1] demonstrated that, in Caucasians with untreated obstructive sleep apnoea (OSA), continuous positive airway pressure (CPAP) can improve baroreceptor responsiveness and reduce waking blood pressure within 6 weeks, but that this treatment period was insufficient to modify insulin resistance or change the metabolic profile. This is the first randomised placebo-controlled blinded crossover trial comparing cardiovascular and metabolic outcomes after 6 weeks of therapeutic and sham CPAP in obese symptomatic Caucasians with OSA. We have found similar CPAP effects in obese Japanese OSA patients (table 1). The authors suggested that there is a need to offer multiple modalities of treatment to obese OSA patients if their cardiovascular risk profile is to be successfully modified. We totally agree with their conclusion. However, it may be necessary to address the following unresolved issues.

1) Although the participating OSA subjects were randomised to receive either therapeutic or identical sham CPAP, sham CPAP may not be the best placebo treatment. Although therapeutic CPAP improves sleep quality in OSA patients, sham CPAP may not always improve sleep quality and daytime function in patients [2]. Healthy individuals without OSA may experience night-time CPAP as a form of torture. However, patients with severe OSA have a good night's sleep with CPAP.

2) The severity of the OSA may influence the effect of CPAP on metabolic outcomes. As shown in table 1, CPAP treatment exerted significant effects on some metabolic variables in very severe OSA (apnoea/hypopnoea index (AHI) >45 events·h^{-1}), but not in moderate-to-severe OSA (AHI <45 events·h^{-1}).

3) There is an effect of sex on metabolic outcomes and sleep apnoeas [3]. Risk factors for metabolic syndrome also differed by sex; in males, age, body mass index (BMI) and OSA (AHI $\geq$15 events·h^{-1}) were significantly associated with metabolic syndrome, whereas in females, BMI was the only risk factor [4].

4) The effect of short-term withdrawal of CPAP therapy on cardiovascular and metabolic variables may be of interest in

TABLE 1 Effect of 6-week continuous positive airway pressure (CPAP) treatment on components of metabolic syndrome in obstructive sleep apnoea (OSA)

	Severe OSA#		Nonsevere OSA¶	
	Good compliance+	Poor compliance§	Good compliance+	Poor compliance§
Subjects n	42	20	32	20
AHI events·h^{-1}	55.7±2.0	53.1±2.4	31.7±1.8	30.7±2.2
ΔAHI events·h^{-1}	-50.9±2.4*	-31.1±2.4*	-26.7±1.1*	-18.7±2.1*
ESS	15.2±0.4	14.7±0.9	11.7±0.9	11.2±0.5
ΔESS	-11.2±0.4*	-7.8±0.9*	-7.2±0.9*	-4.8±0.5*
BP mmHg				
Systolic	145.7±2.0	143.4±2.1	138.7±2.0	137.5±2.4
Diastolic	86.1±1.5	86.7±1.6	86.7±1.6	86.7±1.6
ΔSBP	-10.1±1.5*	-6.6±1.7*	-6.1±1.5*	-2.6±1.7
FPG mM	4.6±0.1	4.7±0.1	4.6±0.1	4.5±0.1
FPG mM	-0.2±0.1	-0.1±0.1	-0.2±0.1	0.1±0.1
HOMA-IR	3.5±0.4	3.4±0.5	3.1±0.4	3.0±0.5
ΔHOMA-IR	-0.2±0.1	-0.1±0.1	-0.1±0.1	0.1±0.1
Cholesterol mM	5.6±0.1	5.5±0.1	5.6±0.1	5.5±0.1
ΔCholesterol mM	-0.2±0.1	-0.1±0.1	-0.1±0.1	0.1±0.1
Triglycerides mM	1.9±0.2	1.8±0.2	1.9±0.3	1.9±0.2
ΔTriglycerides mM	-0.1±0.1	0.0±0.1	-0.1±0.1	0.1±0.1

Data are presented as mean±SEM. AHI: apnoea/hypopnoea index; Δ: change (post-CPAP value minus pre-CPAP value); ESS: Epworth Sleepiness Scale; BP: blood pressure; SBP: systolic BP; FPG: fasting plasma glucose; HOMA: homeostasis model assessment; IR: insulin resistance. #: AHI ⩾45 events·h^{-1}; ¶: 45 events·h^{-1}>AHI⩾15 events·h^{-1}; +: >5 h·night^{-1} CPAP; §: <5 h·night^{-1} CPAP. *: $p<0.05$ *versus* pre-CPAP value.

OSA patients. This inverse method may also confirm the randomised placebo-controlled blinded crossover trial results. It was recently reported that 1 week of CPAP withdrawal is associated with a return of OSA and a marked increase in sympathetic activity without concomitant elevation of vascular inflammatory marker levels [5]. Therefore, effects of CPAP treatment and its withdrawal may differ between cardiovascular function and metabolic and inflammatory function as a function of time.

5) The relationships between metabolic variables and systemic inflammation and sympathetic activity are complex [6]. There is a positive correlation between interleukin (IL)-6 or tumour necrosis factor (TNF)-α plasma levels and BMI. IL-6, TNF-α and insulin levels are elevated in sleep apnoea independently of obesity and visceral fat [7, 8]. Conversely, recent data suggest that OSA has no independent association with lipid abnormalities, insulin resistance, and serum leptin and adiponectin levels. On multivariate analysis, obesity was the major determinant of metabolic abnormalities [9].

Furthermore, there is a maladaptive autonomic response of chemoreceptors, reacting to the hypoxia, hypercapnia and acidosis of sleep apnoea in OSA patients. The elevated sympathetic response triggers an inflammatory cascade that results in a myriad of downstream consequences, including insulin resistance, hypertension, diabetes, atherosclerosis and metabolic syndrome. The sympathetic bias and endocrine disturbances may further exacerbate sleep disturbance in a potentially pernicious cycle.

6) Poor compliance with CPAP may considerably affect metabolic outcomes [10]. Unfortunately, compliance with CPAP was generally very low in the population-based sample. Furthermore, the patients with more severe OSA may show greater CPAP use than those with mild-to-moderate OSA. Both compliance with CPAP and patient selection may have affected the results of the current study.

Even though we totally agree with the main results of the study by COUGHLIN *et al.* [1], changes in cardiovascular and metabolic variables following CPAP treatment may differ. Although more detailed results from a broad-ranging population with OSA are needed, OSA and its related metabolic abnormalities should be treated by means of CPAP and other useful modalities, including statins, angiotensin II receptor blockers, *etc.*

We believe that continuous positive airway pressure treatment is effective at reducing cardiovascular events through reduced blood pressure, decreased sympathetic activity and reduced systemic inflammation [10]. However, the relative contributions to the reduction in cardiovascular events should be further elucidated in terms of obstructive sleep apnoea severity and the basic mechanisms of metabolic syndrome.

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STATEMENT OF INTEREST

None declared.

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INCREASE IN OXIDATIVE STRESS LEVELS IN ELDERLY PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME: EFFECTS OF AGE AND SEX

To the Editor: Obstructive sleep apnea syndrome (OSAS) has emerged as an important risk factor for cardiovascular disease.[1–3] Although sleep apnea increases with age, the pathological role of OSAS has not been completely established in elderly people. OSAS-induced hypoxic and oxidative stress have been implicated in the increase in circulating inflammatory mediators, including adhesion molecules, inflammatory cytokines, and high-sensitivity C-reactive protein, leading to hypertension and cardiovascular events.[4] The fluctuations in the level of oxygen saturation can be considered analogous to recurrent episodes of ischemia-reperfusion injury, which causes damage after the restoration of blood flow to ischemic or hypoxic tissues. In patients with untreated OSAS, an increase in the production of reactive oxygen species (ROS) and plasma lipid peroxides and a reduced antioxidant capacity have been demonstrated.[5,6] Although oxidative stress increases with age,[7] the effects of age and sex on the oxidative stress in OSAS patients have not been elucidated. It was hypothesized that the increase in age and the severity of OSAS might be correlated with oxidative stress. In the current study, oxidative stress was assessed based on urinary levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a marker of deoxyribonucleic acid (DNA) oxidation in vivo.

Age-dependent differences in urinary levels of 8-OHdG were examined in patients with OSAS. The experimental group consisted of 80 middle-aged (<60) and 80 elderly (≥ 60) patients with OSAS; their age and body mass index (BMI) matched those of the individuals in the control group comprising 80 middle-aged and 80 elderly subjects without OSAS. The patients had to fulfill the following criteria: no renal or renovascular hypertension, systolic blood pressure (BP) less than 160 mmHg or diastolic BP less than 95 mmHg, no chronic renal or hepatic disease, and no diabetes mellitus. Patients with a history of smoking or systemic infections at the time of the study or in the 4 weeks before the study were excluded. No patients were treated using antihypertensive agents. The subjects were examined using polysomnography (PSG) and classified as control subjects based on the apnea–hypopnea index (AHI). In this study, to assess OSAS-induced hypoxia quantitatively, the oxyhemoglobin desaturation index (ODI) was used as previously described (90%).[4] ODI was defined as $DI = \Sigma(90 - SaO_2)\ t$, where t represents the time of desaturation. The urinary excretion levels of 8-OHdG and sleep study variables were compared. Moreover, the correlations between various parameters of OSAS, including the ODI, and oxidative stress in middle-aged and elderly patients with OSAS, were evaluated. All urine and serum samples were collected in the morning between 7:30 and 8:00 a.m. after the PSG examination. The 8-OHdG concentration was determined using an enzyme-linked immunosorbent assay (ELISA) kit (Japan Institute for the Control of Aging; Nikken SEIL Corporation, Fukuroi, Shizuoka, Japan), and urinary creatinine concentration was determined using a standard automated colorimetric assay. Thereafter, urinary 8-OHdG level was normalized for urinary creatinine level and is presented as urinary 8-OHdG (ng/mL):creatinine (mg/mL) ratio. A stable correlation between spot urine levels and 24-hour excretion levels of 8-OHdG has already been established (Table 1).[8]

There were no significant differences in BMI between patients and control subjects in each age group, although AHI in the OSAS group was markedly higher than in the control group. There were no significant differences in BP or metabolic indices. The AHI values in the elderly (50.1 ± 3.2 events/h) and middle-aged (51.6 ± 3.0 events/h) patients with OSAS were considerably greater than those for the age-matched controls (3.8 ± 0.3 and 3.6 ± 0.4 events/h, respectively). There were significant differences in baseline ODI values between the OSAS patients and controls, suggesting that the OSAS patients were exposed to a significantly greater degree of hypoxia than the control subjects. There were no differences in ODI value between the middle-aged and elderly OSAS patients.

The uncorrected values of 8-OHdG levels in urine partially collected during the early morning hours in middle-aged and elderly patients with OSAS were significantly greater than those in the age- and BMI-matched controls. The creatinine-corrected values in all the patients with OSAS were also greater than those in the controls, although age did not affect the urinary excretion levels of 8-OHdG in patients with OSAS. In contrast, the creatinine-corrected 8-OHdG values in elderly women (5.6 ± 1.1 ng/mL) were greater than those in middle-aged women (4.4 ± 0.9 ng/mL) in the control group. This age-dependent difference in 8-OHdG levels was not observed in the female patients with OSAS, and no age-dependent differences in 8-OHdG levels were observed between male controls and male patients.

A positive relationship was noted between 8-OHdG levels and AHI or the magnitude of arterial oxygen desaturation, as indicated by ODI. This significant correlation is observed more clearly between 8-OHdG levels and hypoxic episodes (ODI) (correlation coefficient (r) = 0.389, $P < .01$) than between 8-OHdG levels and apnea episodes (AHI) ($r = 0.249$, $P < .05$).

These results indicate that oxidative stress, as indicated by urinary 8-OHdG excretion level, increased with age in obese females without sleep apnea but was not observed in

Table 1. Urinary 8-Hydroxy-2′-Deoxyguanosine (8-OHdG) Levels and Other Variables in Elderly and Middle-Aged Subjects with Obstructive Sleep Apnea Syndrome (OSAS) and Controls

Variable	Middle-Aged Group with OSAS (n = 80)	Elderly Group with OSAS (n = 80)	Middle-Aged Control Group (n = 80)	Elderly Control Group (n = 80)
	Mean ± Standard Error			
Age	46.8 ± 2.2	65.8 ± 2.2	45.1 ± 2.2	64.8 ± 2.1
Body mass index, kg/m^2	33.4 ± 0.9	32.1 ± 0.9	32.8 ± 1.1	31.5 ± 1.1
Systolic blood pressure, mmHg	138.1 ± 3.7	139.1 ± 4.7	135.6 ± 4.1	137.1 ± 3.7
Diastolic blood pressure, mmHg	82.1 ± 3.2	80.1 ± 3.2	78.9 ± 3.8	78.1 ± 2.8
Total cholesterol, mg/dL	202.9 ± 7.9	199.1 ± 6.9	202.9 ± 7.9	198.3 ± 10.8
High-density lipoprotein cholesterol, mg/dL	43.0 ± 2.2	41.0 ± 2.1	43.6 ± 2.3	42.2 ± 2.1
Triglyceride, mg/dL	144.1 ± 10.7	137.1 ± 12.7	140.1 ± 10.7	132.0 ± 10.9
Fasting plasma glucose, mg/dL	98.4 ± 1.3	94.6 ± 1.3	97.6 ± 1.4	90.3 ± 1.1
Hemoglobin A1c, %	5.7 ± 0.1	5.8 ± 0.1	5.6 ± 0.1	5.27 ± 0.1
Total sleep time, minutes	368.1 ± 20.3*	348.1 ± 20.3*	440.3 ± 20.9	414.3 ± 20.9
Apnea–hypopnea index, events/h	51.6 ± 3.0*	50.1 ± 3.2*	3.8 ± 0.3	3.6 ± 0.4
Lowest oxygen saturation, %	67.2 ± 2.1*	68.9 ± 3.0*	95.8 ± 0.5	94.1 ± 0.5
Oxyhemoglobin desaturation index	2.45 ± 0.32*	2.41 ± 0.36*	0.02 ± 0.01	0.02 ± 0.01
Arousal index/h	42.4 ± 3.1*	40.2 ± 2.2*	8.3 ± 3.1	8.3 ± 3.1
8-OHdG, ng/mL	16.3 ± 3.7	17.1 ± 4.1*	7.8 ± 1.9	8.9 ± 2.1
8-OHdG/Cr, ng/mg	9.7 ± 1.9	10.1 ± 2.1*	4.7 ± 0.9	5.3 ± 1.1

There were 40 men and 40 women in each group.
*P<.001 versus control group.
8-OHdG/Cr = creatinine-corrected 8-OHdG.

obese males without sleep apnea. Furthermore, greater DNA oxidation in elderly patients with OSAS was observed to a considerable extent and in a similar manner, than in middle-aged patients with OSAS, irrespective of sex. This is because urinary 8-OHdG excretion levels were significantly correlated with severity of hypoxia as indexed according to ODI. The greater oxidative stress resulted from the considerable hypoxic stress rather than the apnea episode itself.[9] Age-dependent differences in 8-OHdG levels were observed in the female control subjects but not in female patients with OSAS. Thus, the augmented increase in 8-OHdG secretion caused by severe nocturnal hypoxemia and oxidative stress due to OSAS may overcome the age-dependent increase in 8-OHdG levels in elderly patients with OSAS.

Because life-threatening diseases such as arteriosclerosis and cancer and senescence may be induced and progress as a result of oxidative stress due to ROS, the reduction of oxidative stress is important to prevent the incidence of these events. Although the pathological role of sleep apnea in cardiovascular events and mortality in elderly patients with OSAS remains controversial, the current study indicates that elderly patients are exposed to significant oxidative stress due to sleep apnea–related nocturnal hypoxemia.

Treatment with continuous positive airway pressure (CPAP) greatly reduces hypoxic stress in patients with OSAS. Thus, the treatment of OSAS with CPAP may be clinically effective for the prevention of cardiovascular complications even in elderly OSAS patients, irrespective of sex.

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ACKNOWLEDGMENTS

Conflict of Interest: This work was supported in part by a research grant from Mitsui Life Social Welfare Foundation Japan fund and by a research grant from Mitsukoshi Health and Welfare Foundation in Japan. There is no conflict of interest regarding the present study.

Author Contributions: Study concept and design: Shinji Teramoto and Yasuhiro Yamaguchi. Acquisition of subjects and data, analysis: Hiroshi Yamamoto, Yoko Hanaoka, Masaki Ishii, Hibi Shinichiro. Interpretation of data: Haruki Kume and Masahiro Akishita. Preparation of manuscript: Yasuyoshi Ouchi.

Sponsor's Role: No sponsor in this study.

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DIAGNOSTIC ACCURACY OF CRITERIA FOR URINARY TRACT INFECTION IN NURSING HOMES

To the Editor: The article by Juthani-Mehta et al.[1] illustrates the dilemma facing clinicians taking care of residents of long-term care facilities (LTCFs). As the authors proposed, "a different combination of existing clinical criteria and geriatric manifestations will be more accurate." The challenge is how to differentiate the clinical manifestations of urinary tract infection (UTI) from coexisting comorbidities in older adults.

One study of 284 geriatric patients with UTI in the emergency department considered the following symptoms as possible manifestations of UTI: abdominal pain, nausea, vomiting, decreased appetite, dizziness, malaise, weakness, confusion, falls, and mental status changes.[2] Most of the symptoms, if not all, are based on clinical observation and have not been validated by clinical research studies. In addition, these symptoms are clearly nonspecific, although findings from other studies suggest an indirect link between episodes of falls and UTI, because older adults with UTI may experience delirium, which can lead to falls and fractures. A prospective study of 199 patients in five residential care facilities during 1 year of follow-up revealed that delirium and acute UTI were considered major factors precipitating falls.[3] A case-control study of 335 residents living in an LTCF revealed that altered mental state was recognized as the most important risk factor for injury in those who fell,[4] although a direct link between falls and UTI has not been demonstrated.

The effect of UTI on the functional capacity (e.g., oral intake, activities of daily living) of residents of LTCFs is not clear. A prospective study of 1,324 residents in 39 nursing homes in western Switzerland examined the relationship between infections and functional impairment (defined as death or a decreased activity of daily living score at the end of each follow-up period) in residents of LTCFs during a 6-month follow-up period.[5] This study revealed that infection appeared to be a cause and a consequence of functional impairment in nursing home residents, although subgroup analyses based on the type of infection revealed no significant increase in the risk of functional impairment for UTI. A 3-month period between functional assessments in this study may not have been sufficiently sensitive to detect transient changes in functional status during an episode of UTI.

Because of their nonspecific nature, apart from local urinary tract symptoms and fever, geriatric manifestations of UTI in elderly people in LTCFs may not be sufficient to differentiate UTIs from other coexisting disorders. Presently, the individual healthcare provider must make the final judgment as to when to order urinalysis and whether a patient with bacteriuria has a UTI and should therefore receive antibiotics.[6] More evidence-based studies are needed to clarify this dilemma facing clinicians in the care of elderly people in the long-term care setting.

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ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklists provided by the author and has determined that none of the authors have any financial or any other kind of personal conflicts with this letter.

Author Contributions: Dr. Gau is responsible for the letter. Dr. Clay contributed to the editing and preparation of the letter.

Sponsor's Role: None.

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THE AGING POPULATION AND DEVELOPMENT OF GERIATRICS IN CHINA

To the Editor: We read with great interest the article by Flaherty et al.,[1] in which they provided an overview of the population demographics and healthcare statistics in the People's Republic of China focusing on the older Chinese population, its current care system, and geriatrics. We appreciate the authors and the Journal for the interest in introducing the largest aging population in world to the American geriatrics community. In addition to congratulating the authors' accomplishment of such an overview, we have the following comments.