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LETTERS TO THE EDITOR

ANTIPLATELET CILOSTAZOL, AN INHIBITOR OF TYPE III PHOSPHODIESTERASE, IMPROVES SWALLOWING FUNCTION IN PATIENTS WITH A HISTORY OF STROKE

To the Editor: Stroke patients with dysphagia have a high incidence of aspiration, which may lead to pneumonia.[1] Several investigators have reported that cilostazol, a potent inhibitor of type III phosphodiesterase, reduces the incidence of aspiration pneumonia in patients with a history of stroke,[2,3] but the mechanism by which it does so has not been completely elucidated.

It has been proposed that swallowing disorders play a significant role in the development of pneumonia in patients with a history of stoke;[4,5] therefore, it was hypothesized that cilostazol may improve swallowing function in such patients by exerting pleiotropic effects through inhibiting type III phosphodiesterase. The effects of cilostazol administration on the serum and induced sputum levels of substance P, a transmitter in the nucleus of the solitary tract in the brainstem, were examined, because a significant association between systemic or airway depletion of substance P and silent aspiration and swallowing disorders has been reported in poststroke patients.[6,7]

The study subjects included patients with a 1- to 6-month history of noncardioembolic cerebral infarction confirmed using computed tomography or magnetic resonance imaging. In 48 male patients (mean age ± standard deviation 68 ± 5), swallowing function was examined before and after the administration of cilostazol and compared with swallowing function after the administration of aspirin. This study was a double-blinded, placebo-controlled, three-period crossover study wherein cilostazol administered at a dose of 200 mg twice daily and aspirin administered at a dose of 200 mg/d were compared with placebo. Patients were evaluated at baseline and after 4 weeks of treatment with each drug; a 4-week washout period was allowed after the completion of treatment with each drug. Swallowing function was examined using a repetitive saliva swallowing test and a swallowing provocation test.[4,5] In brief, the ability to swallow voluntary was quantitatively measured for 30 seconds. The swallowing reflex was induced by injecting a bolus of 1 mL of distilled water into the suprapharynx through a 5-Fr small nasal catheter with the patient in the supine position. The swallowing reflex was evaluated as the latency of the response.

The serum and induced sputum levels of substance P were measured using a radioimmunoassay.[8] After administering 5% saline solution via an ultrasonic nebulizer for 15 minutes, blood and induced sputum samples were collected between 7:30 and 8:00 a.m. before and after the completion of the cilostazol and aspirin treatments.

The significance of differences between the groups was assessed using analysis of variance, followed by *t*-tests with Bonferroni correction. The results are expressed as means ± standard deviations, and values of $P<.05$ were considered to indicate statistical significance.

Forty-eight patients completed the study. The latent time of swallowing reflex significantly improved after the administration of cilostazol but not after the administration of aspirin (Figure 1). Cilostazol increased the frequency of voluntary swallowing in 30 seconds (from 4.9 ± 0.2 to 5.6 ± 0.2), but aspirin did not (from 4.9 ± 0.2 to 5.1 ± 0.2). The induced sputum and serum substance P levels also improved after cilostazol administration sputum: from 16.6 ± 3.4 to 30.1 ± 6.2 pg/mL; serum: from 28.2 ± 4.4 to 44 ± 5.2 pg/mL) but not after aspirin administration (sputum: from 16.6 ± 3.8 to 18.1 ± 4.4 pg/mL; serum: from 28.2 ± 4.4 to 30.6 ± 4.6 pg/mL). No obvious untoward effects were observed.

The present study indicated that cilostazol but not aspirin improved swallowing reflex in patients with a history of stroke. Cilostazol also increased airway and systemic substance P levels in these patients. Thus, the improvement in swallowing function may contribute to the reduction in the incidence of pneumonia in poststroke patients treated with cilostazol.

Substance P is a transmitter in the nucleus of the solitary tract in the brainstem, and its level in induced sputum and blood is considerably associated with the swallowing function.[6,7] In experimental data, cilostazol has been reported to increase cyclic adenosine monophosphate (cAMP)-responsive element binding protein (CREB) phosphorylation, leading to upregulation of several apoptotic and dopaminergic genes.[9] This pathway may be involved in the improvement in swallowing function through the increase in substance P level in such patients.

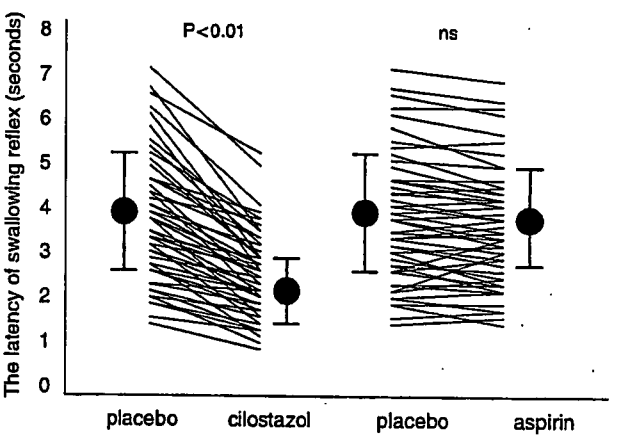

Figure 1. Effects of cilostazol and aspirin on swallowing reflex in patients with a history of stroke. The latency of swallowing reflex (seconds) was examined after 4 weeks administration of cilostazol, aspirin, and placebo. ns = nonsignificant.

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The other mechanism underlying the improvement in swallowing function may be associated with saliva secretion, which the cAMP signaling pathway in the salivary acinar cells mediates.[10] The cilostazol-activated CREB plays a critical role in protein secretion from the parotid acinar cells. Increased saliva production by cilostazol may improve the swallowing function in these patients.

In conclusion, the potent inhibitor of type III phosphodiesterase—cilostazol—improves swallowing function through increased production of substance P in poststroke patients.

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LETTERS TO THE EDITOR

HIGH LEVELS OF CIRCULATING SOLUBLE CD40 LIGAND IN ELDERLY PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME: EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE

To the Editor: Patients with obstructive sleep apnea syndrome (OSAS) have a greater prevalence of coronary artery disease, myocardial infarction, nocturnal angina, and myocardial ischemia.[1–3] Although sleep apnea increases with age, the pathological role of OSAS has not been completely established in elderly people. One of the mechanisms implicated in vascular morbidity in adult patients with OSAS involves changes in nitric oxide pathways.[4,5] A soluble CD40 ligand (sCD40L) is an another marker for endothelium-related activation and dysfunction. This protein binds CD40 on the surface of various cell types of cells and triggers the increased expression of inflammatory mediators, growth factors, and the procoagulant tissue factor. The higher levels of sCD40L essentially indicate a greater risk of a variety of cardiovascular disorders. Furthermore, sCD40L levels were found to be higher in nonobese children with OSAS as well as adult patients with OSAS,[6,7] although circulating sCD40L concentrations and the therapeutic response of sCD40L to continuous positive airway pressure (CPAP) treatment have not been examined in elderly patients with OSAS.

We examined age-dependent differences in circulating levels of sCD40L in patients with OSAS. The experimental group consisted of 80 middle-aged (aged <60) and 80 elderly (60) patients with OSAS matched according to age and body mass index (BMI) to a control group of 80 middle-aged and 80 elderly subjects without OSAS. Subjects had to fulfill the following criteria: no renal and 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 taking antihypertensive agents. The subjects were examined using polysomnography (PSG) and classified as control subjects based on and apnea-hypopnea index (AHI) less than 5. In this study, to assess OSAS-induced hypoxia quantitatively, we used the oxyhemoglobin desaturation index (ODI) as previously described[4] (i.e., 90%). ODI was defined as $DI = \Sigma(90 - \text{oxygen saturation})t$, with t representing the time of desaturation in hours. Circulating sCD40L levels and sleep study variables were compared. Levels of circulating high-sensitivity C-reactive protein (hsCRP), which is a useful inflammatory marker in OSAS, were also examined as previously described.[8,9] The correlations between various parameters of OSAS, including ODI and oxidative stress, were also evaluated. Fasting blood samples were drawn using venipuncture in the morning between 7:30 a.m. and 8:00 a.m., after the PSG examination, into ethylenediaminetetraacetic acid—containing tubes. Blood samples were immediately centrifuged and frozen at -80°C until assay. Plasma levels of sCD40L were assayed with a commercially available enzyme-lined immunosorbent assay kit (BMS 235, Bender MedSystems GmbH, Vienna, Austria) with a sensitivity of 7.92 pg/mL. The intra-assay and interassay coefficients of variation were 6.4% and 5%, respectively.

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

sCD40L levels in blood during the early morning hours in middle-aged and elderly OSAS patients were significantly higher than in their age- and BMI-matched controls, although age did not affect circulating sCD40L levels in OSAS patients. The values of hsCRP levels in middle-aged and elderly OSAS patients were significantly greater than those in controls, although there was no significant increase in hsCRP levels in elderly OSAS patients (Table 1).

A positive relationship was noted between circulating sCD40L levels and AHI or the magnitude of arterial oxygen desaturation, as indicated by ODI. This significant correlation was greater between circulating sCD40L levels and hypoxic episodes (ODI) (correlation coefficient (r) = 0.346, $P<.01$) than between circulating sCD40L levels and apnea episodes (AHI) ($r = 0.226$, $P<.05$). CPAP therapy significantly reduced circulating sCD40L in all patient groups.

These results indicate that the systemic inflammation and endothelial dysfunction indicated by high levels of sCD40L were observed in elderly patients with OSAS. Because sCD40L levels were significantly correlated with severity of hypoxia, as indexed according to ODI, the greater oxidative stress resulting from the considerable hypoxic stress rather than the apnea episode itself was in part responsible for the increase in sCD40L levels in elderly patients with OSAS. The improvement of sCD40L levels after treatment with CPAP may be consistent with the reduction in OSAS-related oxidative stress. Age-dependent differences in sCD40L levels and the therapeutic response of sCD40L to CPAP treatment were not observed in patients with OSAS. Similar results were observed in circulating adrenomedullin levels in elderly patients with OSAS,[10] although hsCRP levels in elderly patients with OSAS were

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Table 1. Circulating Soluble CD40 Ligand Levels and Other Variables in Elderly and Middle-Aged Subjects with Obstructive Sleep Apnea Syndrome (OSAS) and Controls

Characteristic	Middle-Aged OSAS Group (n = 80, 40 Male, 40 Female)	Elderly OSAS Group (n = 80, 40 Male, 40 Female)	Middle-Aged Control Group (n = 80, 40 Male, 40 Female)	Elderly Control Group (n = 80, 40 Male, 40 Female)
	Mean ± Standard Deviation			
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	138.1 ± 3.7	139.1 ± 4.7	135.6 ± 4.1	137.1 ± 3.7
Diastolic blood pressure	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, per hour	42.4 ± 3.1*	40.2 ± 2.2*	8.3 ± 3.1	8.3 ± 3.1
Circulating levels of soluble CD40 ligand, ng/mL	6.8 ± 3.7*	7.1 ± 4.1*	3.8 ± 1.2	4.2 ± 1.1
Circulating levels of high-sensitivity C-reactive protein, ng/mL	3.4 ± 1.1*	4.1 ± 2.1	1.6 ± 0.6	2.7 ± 1.4

*$P<.001$ versus control group.

not significantly different from those in elderly controls. hsCRP levels in middle-aged patients with OSAS were slightly but significantly higher than those in middle-aged controls. Because the insidious inflammatory responses were significantly different between middle-aged and elderly patients, there were more confounding factors affecting hsCRP levels in elderly subjects. Although systemic inflammation and cardiovascular events were frequently found in OSAS patients, the polysomnographic parameters and symptomatic variables did not clearly assess these changes. sCD40L, but not hsCRP, levels were associated with OSAS severity in elderly patients. Thus, CD 40 L level may be a better, more-sensitive marker for the practical assessment of inflammatory status and atherosclerotic progression in OSAS than hsCRP in elderly people.

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STATEMENT OF INTEREST

None declared.

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Variation in the tumour necrosis factor-α gene is not associated with susceptibility to Asian COPD

To the Editors:

In a recent issue of the *European Respiratory Journal*, CHAPPELL *et al.* [1] clearly demonstrated that the lack of association with any of the tumour necrosis factor (TNF)-α single nucleotide polymorphisms or haplotypes makes it highly unlikely that polymorphisms in this gene play a major role in susceptibility to chronic obstructive pulmonary disease (COPD).

Their sample sizes were sufficient to elucidate association of TNF-α gene variations with susceptibility to COPD. However, they neglected the effect of ethnicity differences in genetic susceptibility to COPD. The frequency of the TNF-α-308*2 allele in Caucasian control populations (10–17%) is higher than that in Asians (0–8%) [1–10].

Genetic susceptibility to COPD is dependent upon the action of several gene polymorphisms, sex, age and ethnicity [2]. The TNF-α gene is known to have a polymorphic site at position -308. The TNF-α-308*2 allele, which is associated with a higher level of TNF-α production, has been associated with chronic bronchitis, a characteristic part of COPD, in a Taiwanese population [3]. However, the association of a polymorphism of TNF-α with susceptibility to COPD or to tobacco-related airway inflammation has not yet been confirmed in Asians. It was investigated whether the TNF-α-308*2 allele was associated with COPD in a Japanese population using a PCR-based genotyping assay [4]. The TNF-α-308*2 allele was found in one (1.9%) out of 53 patients with COPD and in one (1.5%) out of 65 smoker control subjects without COPD [4]. The frequency of the major allele, *i.e.* TNF-α-308*1, in the smoker control subjects (0.99) was consistent with data reported previously for other Japanese populations, suggesting that the present samples are representative of TNF-α gene polymorphism in the Japanese population [5]. However, there were no differences between COPD patients and smoker control subjects regarding the allele and genotype frequency of TNF-α. Since chronic bronchitis is not exactly the same, in terms of definition and tobacco sensitivity, as pulmonary emphysema, which is a major feature of COPD, it is possible that the TNF-α polymorphism is associated with infection-related bronchitis rather than tobacco-smoke-related alveolar wall destruction. However, most of the TNF polymorphism studies investigating COPD susceptibility revealed negative results for various Asian populations (table 1) [6–9]. Only one group of authors have insisted that the TNF-α-308*2 may be partly associated with the extent of emphysematous changes in patients with COPD [9].

TABLE 1 Association of tumour necrosis factor (TNF)-α gene polymorphism with chronic obstructive pulmonary disease (COPD) in Asian patients in various studies

First author [Ref.]	Race	Subjects n			Gene position	TNF-α A allele frequency %			Association with COPD
		COPD	SC	PC		COPD	SC	PC	
HUANG [3]	Taiwanese	42	42	99	TNF-α-308*2	19	2.4**	5.1**	Significant
ISHII [4]	Japanese	53	65		TNF-α-308*2	1.9	1.5		NS
SAKAO [9]	Japanese	106	110	129	TNF-α-308*2	16.5	8.2**	7.8**	Significant
CHIERAKUL [6]	Thai	57	67		TNF-α-308*2	7.9	4.7#		NS
JIANG [7]	Han Chinese (Beijing)	57	208		TNF-α-308	5.8	3.1¶		NS
HEGAB [8]	Japanese	88	161		TNF-α-308	2	0		NS

A allele: adenine allele (allele 2); SC: smoker control; PC: population control; TNF-α-308*2: position -308 on TNF-α allele 2; NS: nonsignificant. **: $p<0.001$; #: $p=0.14$; ¶: $p=0.131$

Among Caucasian data, most of the TNF-α polymorphism studies investigating COPD susceptibility have revealed negative results. However, several authors have insisted that homozygosity of this allele predisposes the patient to more severe airflow obstruction and a worse prognosis in a small number of COPD cases [10].

Thus it is necessary to study polymorphisms within the tumour necrosis factor-α gene in a large collection of well-characterised Asian chronic obstructive pulmonary disease patients and control subjects, as in the European Union collaborative project [1]. However, these collective data strongly suggest that tumour necrosis factor-α gene polymorphism does not play a major role as a genetic risk factor for chronic obstructive pulmonary disease in either Caucasian or Asian individuals. However, the tumour necrosis factor-α gene polymorphism may be associated with functional impairment or prognosis in chronic obstructive pulmonary disease.

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STATEMENT OF INTEREST

None declared.

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LETTER TO THE EDITOR

Reference values for 6-min walk distance in Asian adults may not be different from that of Caucasian adults

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In a recent issue of *Respirology*, Poh and coworkers demonstrated that the 6-min walk distance (6MWD) in healthy Singaporean adults cannot be predicted using the reference equations derived from Caucasian populations. Published equations derived from Caucasian subjects overestimated 6MWD in Singaporean Chinese.[1] This is very important research that will assist in the interpretation of 6MWD in Asian patients with cardiopulmonary disease, as the 6MWD reference values have mostly been published for healthy Caucasian subjects. We agree with the authors that an adequate reference value for Asian peoples is necessary for assessing physical function in middle-aged and older patients with COPD.

However, the authors did not fully review the published studies on the 6MWD reference values in Japanese people.[2,3] The 10-min walk distance (10MWD) test was developed by the Japanese Research Group for Chronic Respiratory Failure to determine the 10MWD reference values for healthy male and female Japanese adults.[2] From these values, the mean 6MWD value for healthy Japanese men and women are approximately 572 m and 504 m, respectively. One hundred and fifty-eight healthy subjects were also evaluated for 6MWD using three walking tests with a standardized protocol. Mean values of 6MWD for healthy male and female Japanese adults are 624 m and 541 m, respectively. These data are not all that different from the authors' data or from Enright and Sherrill's data.[4] As such we do not think that the reference values show a big difference between Asian and Caucasian populations (Table 1).

Moreover, there are considerable variations of 6MWD references even in the Caucasian population. Enright and coworkers have reported that the mean 6MWD in a healthy subset of participants was 367 m for elderly women and 400 m for elderly men using a sample from the Cardiovascular Health Study.[5] The equations predict distances of 430 m and 464 m for a 67-year-old white woman and man of average height and weight, respectively. This reference equation gives predicted (mean) 6MWDs that are substantially lower than those published by previous investigators on Caucasian populations.[6–8]

Troosters and coworkers have reported that the mean values for 6MWD for healthy elderly men and women are 673 m and 589 m, respectively.[6] A study of 290 healthy adults in Tucson, USA predicts distances of 466 m and 544 m for women and men, respectively.[4] Rikli and Jones have examined 6MWD in 7183 older adults. Their predicted values are approximately 50% greater than Enright's data.[7]

The reasons why these reference equations are so different in healthy volunteers in either Caucasian or Asians are not clear. Differences in participant recruitment and test instructions may account for the variations among different studies. The American Thoracic Society has published detailed guidelines for 6MWD procedures that should be followed by investigators studying carefully selected healthy people.[8] It has been also cautioned that the reference equations obtained from this model explained only 20% of the variation in 6MWD.[5] According to the American Thoracic Society review of previously published 6MWD studies, the increases due to the learning effect ranged from a mean of zero to 17%. Performance usually reaches a plateau after two tests performed within a week. The reproducibility results from one study of 112 patients with stable, severe COPD suggest that an improvement of >70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant.[9]

Considered together with the data between test variation and intra-test variation there is no definite reference value of 6MWD in either Caucasian or Asians.

The 6MWD testing should be useful for measuring changes in functional status in the clinical setting, but considerable caution is needed when using currently available reference equations to determine if a given

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Table 1 The mean value of 6-min walking distance in male and female Asians and Caucasians

Author (ref. no)	Poh (1)	Takishima (2)	Teramoto (3)	Enright (4)	Enright (5)	Troosters (6)	Rikli (7)
Race	Asian	Asian	Asian	Caucasian	Caucasian	Caucasian	Caucasian
Mean age (years)	61	65	65	60	67	65	
Male							
6MWD (m)	580	572	624	576	464	673	689
Subjects (*n*)	16	34	80	117	715	54	7183†
Female							
6MWD (m)	538	504	541	494	430	589	624
Subjects (*n*)	19	38	78	173	1094	54	

†Total number of subjects of male and female.
6MWD, 6-min walking distance.

patient's 6MWD is normal or low. Expected values should be adjusted for the patient's age, gender, height and weight.

In summary, there is considerable variation in the normal values of 6MWD even in healthy people. The published reference equations may help in the assessment of functional status in patients with cardiopulmonary diseases, but not necessarily determine the absolute exercise capacity in these patients. The variation in 6MWD is affected by a number of factors that are not solely due to race and ethnicity.

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complaints were diagnosed with bronchitis. This resulted in a more frequent use of inhaled steroids and bronchodilators in Dutch children as compared with German children [2].

We cannot exclude the fact that a possible geographically heterogeneous worldwide *Chlamydia pneumoniae* pandemic could contribute to changes in asthma prevalences in different countries. However, it seems unlikely to us that this would be the sole explanation, as not all asthmatics (established or newly diagnosed) have *C. pneumoniae* present in bronchoalveolar lavage fluid. Moreover, the widespread use of (macrolide) antibiotics has not prevented a clear increase in asthma prevalence. On the contrary, it seems that a decrease in hospitalisation and mortality is strongly associated with an increase in the use of inhaled steroids [3], and there is no indication that this is associated with the use of antibiotics.

However, it is certainly worthwhile to pay attention to the so-called Chlamydia-asthma theory proposed by D.L. Hahn and to investigate the presence of *Chlamydia pneumoniae* or other infectious organisms in new asthma patients.

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Nasogastric tube feeding is a cause of aspiration pneumonia in ventilated patients

To the Editors:

In a recent issue of the *European Respiratory Journal*, KOSTADIMA *et al.* [1] reported that early gastrostomy is associated with a lower frequency of ventilator-associated pneumonia (VAP) compared with nasogastric tube (NGT) feeding in patients who are mechanically ventilated due to stroke or head injury. Since VAP is the most frequent and serious intensive care unit (ICU)-acquired infection among patients undergoing mechanical ventilation, and is associated with a 20–30% increase in the risk of death, the preventive strategy for VAP in mechanically ventilated patients is important to reduce the length of an ICU stay and overall mortality [2].

Although the classic theories, including the gastropulmonary hypothesis, are important to understand the mechanisms of VAP, the recent advancement of the pathophysiology of nosocomial pneumonia and aspiration pneumonia are not fully discussed in the paper by KOSTADIMA *et al.* [1].

There is growing evidence that oropharyngeal dysphagia plays a critical role in aspiration pneumonia and VAP in mechanically ventilated patients [3, 4]. Brain injury, severe stroke and unconsciousness, due to sedatives and hypnotics, disturb the swallowing reflex. This results in the development of aspiration pneumonia in humans and animals [5]. However, nosocomial pneumonia and aspiration pneumonia are prevented by the improvement of the swallowing reflex after administration of angiotensin-converting enzyme (ACE) inhibitors [6]. The elevated levels of bradykinin and substance P by ACE inhibitors play a role in setting the threshold for the cough and swallowing reflex in humans, resulting in the reduction of occurrence of pneumonia. Although KOSTADIMA *et al.* [1] speculated about the underlying mechanisms of risk of VAP in the patients with NGT feeding, they did not assess the swallowing reflex and cough reflex. We have developed a novel diagnostic test for the risk of aspiration pneumonia [7, 8]. The simple swallowing provocation test can be applied for all the ventilated patients as it is very easy and can be performed on bedridden patients without requiring their cooperation. The assessment of the swallowing reflex is the clue to the underlying mechanisms of VAP in critically ill patients. As it has been suggested that nosocomial maxillary sinusitis increases the occurrence of VAP, microaspiration of oropharyngeal materials, including maxillary sinus, is a significant cause of VAP [9].

NGT feeding is known to be a significant cause of aspiration pneumonia in stroke patients [10]. Since the NGT bypasses the small amount of gastric contents through to the oropharynx, the materials can be easily aspirated into lower airways in dysphagic patients with stroke. The mechanism is not related to the percutaneous endoscopic gastrostomy (PEG). This evidence supports the fact that NGT feeding, but not PEG, is a significant cause of VAP in critically ill patients. Although feeding *via* PEG is a very straightforward way to reduce aspiration and aspiration-associated pneumonia, the improvement of the swallowing reflex must be a fundamental approach to reduce VAP in patients. As the PEG procedure using gastroscopic fibre may also be a risk for aspiration in unconscious patients, the indication of early gastrostomy for

the patients should be very carefully assessed. The PEG feeding patients with dysphagia may be suffering from aspiration pneumonia [11].

Considered together, we believe that the prevention of aspiration by using oral care, angiotensin-converting enzyme inhibitors and swallowing rehabilitation may be an alternative approach in reducing the risk of ventilator-associated pneumonia in patients.

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From the authors:

We read with interest the letter from S. Teramoto and coworkers regarding the role of oropharyngeal dysphagia in the pathogenesis of ventilator-associated pneumonia (VAP). The presence of a nasogastric tube has been identified as an independent risk factor for VAP, mainly because of gastro-oesophageal reflux and aspiration [1, 2]. Aspiration is probably due to loss of anatomical integrity of the lower oesophageal sphincter, increased frequency of transient sphincter relaxation and oropharyngeal dysphagia *via* desensitisation of the pharyngoglottal adduction reflex [3, 4].

We speculate that the advantage of performing an early gastrostomy is the possibility of avoiding dysfunction of lower oesophageal sphincter due to the presence of a nasogastric tube [5]. JOHNSON *et al.* [6] have demonstrated an increase in lower oesophageal sphincter pressure following performance of percutaneous endoscopic gastrostomy and a decrease in gastro-oesophageal reflux score. Prevention of oropharyngeal dysphagia induced by the nasogastric tube may be another mechanism in reducing the risk of aspiration.

Of note, percutaneous endoscopic gastrostomy does not eliminate gastro-oesophageal reflux, mainly in patients with a pre-existing nasogastric tube [7]. For this reason, we selected the performance of early gastrostomy in our study. In a recent report, MCCLAVE *et al.* [8] found a decrease in the incidence of regurgitation in intensive care unit patients with early gastrostomy compared with those with a nasogastric tube.

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Heart rate variation analysis may not effectively detect sleep apnoeas in heart failure

To the Editors:

In a recent issue of the *European Respiratory Journal*, VAZIR *et al.* [1] demonstrated that spectral analysis of heart rate variations (HRV) may be useful as a "rule-out test" for sleep-disordered breathing (SDB) in patients with mild-to-moderate congestive heart failure (CHF). This is an interesting approach to the diagnosis of SDB in CHF patients without sleepiness. As CHF patients with Cheyne–Stokes respiration (CSR)/central sleep apnoea (CSA) are often asymptomatic, this noninvasive approach may be effective to rule out SDB in patients. However, we feel that there are a number of problems with the article by VAZIR *et al.* [1].

First, HRV analysis cannot be applied in patients with arrhythmia, including atrial fibrillation (AF). In a group of patients with CHF, it has been demonstrated that there is a considerable association between AF and CSA [2]. Thus, AF may be a feature of CHF with CSR/CSA. As AF is very common in CHF with CSR/CSA, it is difficult for HRV analysis alone to rule out the majority of patients with both AF and SDB. Furthermore, paroxysmal AF (PAF) can occur during the night in patients with sleep apnoea and in those of increased age [3]. The presence of PAF episodes and frequent ventricular ectopy may impair the analysis of HRV in patients with CHF.

Secondly, there is the problem of the causal relationship between AF and CSR/CSA. It has been suggested that the risk factors for CSR/CSA are male sex, AF, aged >60 yrs and hypocapnia. AF may therefore be a causal factor for CSR/CSA. In this scenario, CHF patients with AF have a high risk for CSR/CSA. In addition, treatment of arrhythmia with atrial overdrive pacing (AOP) may also have some beneficial effects on sleep apnoea itself [4]. Although obstructive sleep apnoea syndrome predisposes to clinically significant cardiac rhythm disturbances that can be successfully controlled by nasal continuous positive airway pressure, AOP has no significant effect on the respiratory variables, including the apnoea/hypopnoea index [5]. Therefore, the causal relationships between AF and CSR/CSA are not simple.

Thirdly, CHF patients are often treated with antihypertensive agents. These agents also have some effect on HRV results. It has been reported that a sympathetic activation during the day and a decrease in parasympathetic activity during the night after therapy with a calcium channel blockade, amlodipine, correlated with increases in plasma noradrenaline (NA). In contrast, therapy with an angiotensin II receptor blocker, telmisartan, significantly increased parasympathetic activity without changes in NA during the night and day [6]. It has also been suggested that treatment with a nonselective β-adrenergic blocking agent, carvedilol, in CHF restores both autonomic balance and the ability to increase reflex vagal activity [7]. Thus, the treatment strategy for CHF with antihypertensive agents has a great impact on HRV analysis.

Autonomic disturbances and central nervous system abnormality also cause SDB and cardiac dysfunction [8]. Patients with neurological disorders and CHF may not undergo HRV analysis.

The large number of CHF patients cannot all be examined in sleep laboratories, so alternative methods of screening for SDB may be required for CHF patients in AF. Although pulse oximetry may underestimate nondesaturated CSA, it still has an advantage over HRV monitoring in terms of convenient and widely available methods. Thus, CHF patients with negative results in SDB judged by pulse oximetry should be analysed with HRV.

In two previous studies [9, 10], sleep apnoea patients had markedly decreased heart rate variability and increased blood pressure variability. These variability abnormalities are characteristic of patients with hypertension. The abnormalities in cardiovascular variability may exaggerate ventricular function and contribute to development of AF and other cardiovascular diseases [9, 10]. Although cardiovascular variability and HRV abnormality are features of CHF with SDB, the clinical significance of HRV analysis for screening SDB may be limited.

Because an ideal screening test should have a high sensitivity with a reasonable specificity, we believe that the conclusion drawn by VAZIR *et al.* [1] should be changed to: "spectral analysis of heart rate variations may be useful as a noninvasive rule-out test for sleep-disordered breathing in patients with congestive heart failure without arrhythmia."

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From the authors:

We greatly appreciate the comments made by S. Teramoto and co-workers. In our study [1] we suggested that spectral analysis of heart rate in patients with mild-to-moderate heart failure could be of value in ruling out severe sleep-disordered breathing (SDB), and its use could reduce the burden on sleep laboratories screening for SDB in the heart failure population. However, we stressed that further prospective validation was required and discussed in depth the limitations of spectral analysis of heart rate variability (HRV) as a rule-out test for SDB in heart failure. The key limitation is that it cannot be applied to heart failure patients with atrial fibrillation (AF), or those with extensive pacing or excessive ventricular ectopy. Therefore, these groups of patients were excluded for analysis of HRV in our study. Thus, we agree with S. Teramoto and co-workers that a more precise conclusion would be: "spectral analysis of heart rate variation is useful as a rule-out test for SDB in patients with heart failure without significant arrhythmia".

The major advantage of HRV analysis is that it can be used within the cardiology setting, where cardiologists are using a tool that they are much more familiar with than pulse oximetry. Furthermore, heart failure patients who have already undergone Holter monitoring to assess for potential arrhythmias could also have their Holter monitoring analysed for SDB. As we discussed in our paper, the combination of pulse oximetry together with HRV may be a stronger, more comprehensive screening tool for SDB as patients who are paced or who have arrhythmias can be screened for SDB.

We indicated that the presence of SDB is likely to be high in heart failure patients with AF [2], and as HRV analysis cannot be applied to these patients we have suggested that these individuals should be assessed for SDB using pulse oximetry.

S. Teramoto and colleagues raise the issue of the possible effects of medication on the percentage very low frequency index (%VLFI) component of spectral analysis of HRV. There are published data on the effects of medication on other aspects of HRV; however, data on the effects of medication on %VLFI are lacking. In our population of heart failure patients, all patients who underwent HRV analysis were taking angiotensin-converting enzymes or angiotenesin II receptor blocker, and 72% were also taking β-blocker, 12% digoxin and 32% diuretics. Thus, the results from our study also include the possible effects of medications on %VLFI. Furthermore, ROCHE and co-workers [3, 4] published data on %VLFI within patients screened for obstructive sleep apnoea, and a significant number of these patients were on various cardiac medications.

S. Teramoto and co-workers also raise the point that heart failure patients with neurological comorbidity may have abnormalities in the autonomic and central nervous system, which could affect heart rate variability. They suggest that such patients should not undergo heart rate variability analysis. In our study, heart failure patients did not have neurological deficits, so findings cannot be extrapolated to heart failure patients with concurrent neurological deficit. The effect of the presence of abnormal neurology on percentage very low frequency index is unclear and further investigation is required.

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analysis[5] regarding the diagnostic accuracy of determining ADA vs interferon (IFN)-γ showed that IFN-γ is superior to ADA, although the difference is small. Therefore, establishing a diagnosis of tuberculosis pleuritis based only on pleural fluid ADA without pleural biopsy findings is still controversial.[6]

We do not intend to deny the usefulness of pleural fluid ADA for diagnosing tuberculosis pleuritis. Furthermore, we do not insist that pleural fluid INF-γ can replace pleural fluid ADA, or that pleural fluid INF-γ should be measured instead of measuring pleural fluid ADA for diagnosing tuberculous pleuritis. We would like to emphasize the usefulness of the measurement of pleural fluid INF-γ in addition to pleural fluid ADA, especially in low-incidence populations in developed countries, including Japan, because the measurement of IFN-γ is a relatively high-cost test, but has no associated complications.

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Apoptosis of Circulating Neutrophils and Alveolar Macrophages in COPD

To the Editor:

In a recent issue of *CHEST* (May 2004),[1] Noguera and coworkers reported that *in vitro* neutrophil apoptosis in patients with COPD occurred at a rate similar to that found in healthy individuals and smokers with normal lung function. Further, increased surface expression of Mac-1 (CD11b) and decreased surface expression of L-selectin (CD62L) were observed in the apoptotic neutrophils of patients with COPD.

It has been reported that neutrophil granulocytes show a reduced spontaneous apoptosis during acute exacerbations of COPD, but that increases progressively after treatment and clinical remission.[2] This raises the question of the importance of neutrophil apoptosis in the development and resolution of exacerbations of COPD. Thus, the current study may provide some scientific background to address the dynamics of apoptosis *in vivo* lung neutrophils. However, a number of questions remain to be solved.

First, apoptosis is induced by both oxidant production and the depletion of antioxidant in cells. Inversely, supplementation of antioxidant prevents apoptosis in lung-derived cells.[3] Thus, isolated circulating neutrophils from the blood stream that are not fully occupied with blood antioxidant are not a good candidate for the analysis of cell fate in the various inflammatory diseases.

Second, cigarette smoke (CS) contains approximately 4,000 various constituents, including numerous chemicals that result in the production of reactive oxygen species. CS causes apoptosis and necrosis in airway cells including alveolar macrophages (AMs).[4,5] CS-mediated depletion of lung glutathione is thought to lead to increased lipid peroxidation, neutrophil sequestration, and transcription of proinflammatory cytokine genes.[6]

We have reported that CS extract (CSE) induced apoptosis at lower concentrations (10 to 25%) and necrosis at higher concentrations (50 to 100%). We also examined the effects of glutathione S-transferase P1, one of the xenobiotic and antioxidant enzymes in the lung, against the cytotoxicity of CSE. Thus, the antioxidant status and antioxidant gene expression levels may have effects against CS in the airway cells.[7]

Third, although apoptosis is a universal process in the cells, the mechanism of apoptosis is not simple. In *in vitro* studies,[5] human AMs cultured with aqueous CSE undergo apoptosis. This apoptosis is associated with increased oxidative stress, Bax protein accumulation, mitochondrial dysfunction, and mitochondrial cytochrome c release, but is independent of p53, Fas, and caspase activation. These results may provide information to explain macrophage dysfunction and lung diseases in cigarette smokers.

Fourth, patients with bronchiectasis had a lower percentage of neutrophils that were neither apoptotic nor necrotic than in healthy control subjects.[8] The low levels of apoptosis observed in the patients may be associated with inhibition of apoptosis by inflammatory mediators such as interleukin (IL)-8 and tumor necrosis factor (TNF)-α.[9] High levels of TNF-α and IL-8 have consistently been found in the bronchial secretions of the patients. Because these cytokines have been known to be increased in patients with COPD, a similar mechanism may work in patients with COPD. Acute exposure to CS induces infiltration of neutrophils into the airways through nuclear factor-κB and IL-8 gene expression.[10]

Fifth, in COPD, plasma soluble Fas ligand (sFas) was within normal limits. Plasma soluble Fas/Apo-1 receptor (sFas) levels were similar among healthy control subjects, disease control subjects, and patients with mild-to-moderate COPD, but were significantly increased in severe COPD.[11] The increased plasma sFas is independent of hypoxemia, and increases in $PaCO_2$, TNF-α, IL-6, and inflammation may be associated with progression of COPD. Thus, the measurement of apoptosis of AMs and neutrophils in lungs in relation to the different pathologic stages of COPD may offer further information for the role of apoptosis of lung cells in the pathogenesis of COPD.

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Normal Polysomnography in Children and Adolescents

To the Editor:

Ng and colleagues[1] have raised several issues in their comments on our study.[2] Based on the study by Trang et al,[3] they questioned the validity and sensitivity of the thermistor to detect obstructive hypopneas. The use of a nasal cannula to monitor airflow and to detect apneas and hypopneas has become popular in recent years. This technique may be advantageous in many aspects; however, it has limitations. In their article, Trang and colleagues[3] showed that the time spent with an uninterpretable cannula signal was significantly longer than the time spent with an uninterpretable thermistor signal (mean uninterpretable time out of total sleep time for the thermistor, 0%, compared to 2 to 4% for the cannula). In addition, mouth breathing was a frequent cause for cannula signal unreliability. More studies are needed to compare the two techniques before the nasal cannula can become the "gold standard" and the only recommended method. The thermistor has been used in many published pediatric studies from the past few years.[4–7]

We think that the finding that only three subjects had a total of seven obstructive apneas (OAs) [one child had five of the seven OAs] precludes the possibility that the normal distribution of OAs over the 70 cases in the study is possible. Hence, calculating the SD for three cases would be meaningless.

The goal of the study was to establish normal values. Therefore, the study aimed to provide an upper limit value for OAs and obstructive hypopneas, such that all resulting values higher than that number would be considered abnormal. Because only 3 of 70 healthy subjects had a total of seven OAs, calculating the normal upper limit by dividing 7 by the total sleep time of all 70 cases combined will result with an OA index value that would define these three healthy children as abnormal. Using the method described in our study, we presented an upper limit value for the OA index that applies to any child who has OAs.

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appealing and correct, because CPET is both fun (to teach fellows about) and profitable (clinically), providing important diagnostic and clinical insight into pulmonary disease processes that cannot be obtained any other way. CPET is a test modality from which the attending physician will derive insight and benefit. As such, CPET is indeed profitable.

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Obstructive Sleep Apnea Causes Systemic Inflammation and Metabolic Syndrome

To the Editor:

In a recent issue of *CHEST* (July 2004),[1] Ilatipoglu and Rubinstein pointed out that the possibilities of pathophysiologic link between obstructive sleep apnea syndrome (OSAS) and airway and/or systemic inflammation. They suggested that increased levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and high-sensitivity C-reactive protein (hsCRP) are involved in the pathogenesis of systemic inflammation in OSAS. However, the important and growing issue of metabolic syndrome in patients with OSAS is not argued.

OSAS is recently recognized as a risk factor for cardiovascular disorders and metabolic syndrome.[2–6] OSAS is related to obesity, insulin resistance, and diabetes mellitus. In addition, leptin and insulin levels were elevated in patients with OSAS independently of obesity, and visceral fat was the primary parameter linked with sleep apnea. The association of OSAS with insulin resistance and diabetes type 2 has been confirmed.[5,6] Adiponectin is a hormone secreted by adipocytes that acts as an antidiabetic and antiatherogenic adipocytokine. Levels of adiponectin in the blood are decreased under conditions of obesity, insulin resistance, and type 2 diabetes. We have found that plasma level of adiponectin is decreased in OSAS patients compared with that in obese control subjects without OSAS.[7] The level of adiponectin is associated with the severity of OSAS as indicated by apnea-hypopnea index (AIII), rather than obesity indexed as body mass index. The lower adiponectin level is also associated with increased levels of hsCRP and IL-6.[7]

At the inflammatory point of view, the levels of TNF-α, IL-6, hsCRP, adhesion molecules, and monocyte chemoattractant protein-1 were markedly and significantly elevated in patients with sleep apnea than those in normal control subjects.[8,9] IL-6 and hsCRP levels were independently associated with OSAS severity as indicated by the AIII. In addition, hsCRP level is associated with visceral adipose tissue and is significantly associated with the components of insulin resistance syndrome.[5] These data support the belief that inflammatory processes and metabolic syndrome are activated in atherosclerotic lesions in patients with OSAS. C-reactive protein and other inflammatory cytokines accelerate the progression of atherosclerosis in patients with OSAS. In addition, increase in circulating levels of adenosine and urinary uric acid in patients with obstructive sleep apnea are implicated with increased production of reactive oxygen species. Activation of redox-sensitive gene expression is suggested by the increase in some protein products of these genes, including vascular endothelial growth factor, erythropoietin, endothelin-1, inflammatory cytokines, and adhesion molecules.[10,11] These results implicate the participation of redox-sensitive transcription factors as hypoxia-inducible factor-1, activator protein-1 and nuclear factor-κB.

Importantly, the elevated levels of atherogenic inflammatory mediators were improved by the OSAS-specific treatment such as nasal continuous positive airway pressure.[8–11] Thus, OSAS plays a crucial role in metabolic syndrome and systemic inflammatory disorders.

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Insights of Neurologic Dysfunction After Coronary Artery Bypass Grafting

To the Editor:

We read with great interest the article by Ganushchak and associates (June 2004).[1] The authors have investigated the correlation between the combinations of hemodynamic events during cardiopulmonary bypass (CPB) and the development of postoperative neurologic complications. The authors have utilized cluster analysis to review 1,395 perfusion charts, and have concluded that CPB procedures with large fluctuations in hemodynamic parameters have an increased risk for the development of postoperative neurologic complications.

We would like to make a few comments for this important investigation. First, it is well documented that the number of emboli (micro and macro) delivered during CPB has a direct correlation with the postoperative neurologic dysfunction.[2,3] The duration of CPB also has an impact on the number of emboli delivered during CPB; the longer the duration, more emboli delivered.[4] According to Table 2, the duration of CPB was much longer in one group with postoperative neurologic complications (n = 27) compared to the no-complication group (103 ± 43 min vs 82 ± 33 min, p = 0.01 [± SD]). The only way to quantify the number of microemboli during CPB is to use transcranial Doppler (TCD) monitoring. Did Ganushchak and associates use TCD monitoring during CPB?

Second, the authors have used two different hollow-fiber membrane oxygenators in this investigation. One wonders whether or not there was any significant difference between the oxygenators in 27 patients with postoperative neurologic complications. In 27 patients, did the authors calculate how many times one oxygenator was used vs the other oxygenator? Were there any significant differences between the two oxygenators?

Last, the authors have documented that the majority of patients with postoperative neurologic complications (21 of 27 patients) coincide with postoperative cardiac arrhythmias. It is not clear whether the neurologic complications were secondary to cardiac arrhythmias or not. The cause of postoperative neurologic complications in these 21 patients was probably due to ventricular arrhythmias rather the CPB procedure.[5] We congratulate the authors for applying cluster analysis to this particular patient population, and we also believe that large fluctuations in hemodynamic parameters during CPB has caused significant postoperative neurologic risks.[5]

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To the Editor:

First, we thank Drs. Luo and Ündar for their comments on our investigation, and acknowledge them for recognizing the interest and importance of our article. In answer to the first comment, we like to express that we also recognize the fact that the number of emboli (micro and macro) delivered during cardiopulmonary bypass (CPB) could have an impact on the incidence of postoperative neurologic complications. Unfortunately, we were unable to use transcranial Doppler (TCD) routinely in our patients. However, a longer CPB procedure is theoretically accompanied by a higher number of emboli delivered, as was described previously.[1,2] Therefore, although we did not use TCD, one could hypothesize that the aforementioned is confirmed by our findings as presented in Table 2. However, the large difference in number of patients in our study (27 patients with postoperative neurologic complications vs 1,368 patients without neurologic complications) made the results of the analysis of variance test suspicious. That is why we used cluster analyses, and in the sequence of these analyses the impact of duration of CPB on the development of postoperative neurologic complications disappeared. Nevertheless, microremobilization of cerebral vessels during CPB could be one of the factors explaining the significance of fluctuations in hemodynamic parameters in the increased risk for the development of postoperative neurologic complications. It is well documented that good blood flow through the brain might hasten the clearance of microemboli, and increased perfusion pressure during CPB has been proposed as a means of forcing air bubbles through the cerebral microcirculation.[3] It is obvious that fluctuations in perfusion pressure could often provoke the stabilization of an embolus in a cerebral vessel and increase the duration of hypoxia and extend the area of hypoxic damage.

Second, the type of oxygenator indeed could affect the rate of microemboli during CPB[4] and, in this way, be related to the incidence of postoperative neurologic complications. The two types of oxygenators used in our patients were used in sequence. Although the influence of oxygenator type on postoperative neurologic complications was beyond the scope of our study, we evaluated whether there was any significant fluctuation in the frequency of neurologic complications during the study period (between May 1996 and January 1999). This appeared not to be the case, and therefore we assumed that the type of oxygenator had no significant impact on the results as described in our article.

Third, in general, causal relations are extremely hard to prove in clinical research. In this retrospective study, we could not distinguish the sequence of events in complications development.

communications to the editor

Communications for this section will be published as space and priorities permit. The comments should not exceed 350 words in length, with a maximum of five references; one figure or table can be printed. Exceptions may occur under particular circumstances. Contributions may include comments on articles published in this periodical, or they may be reports of unique educational character. Please submit letters online at http://mc.manuscriptcentral.com/CHEST. Please include a cover letter with a complete list of authors (including full first and last names and highest degree), corresponding author's address, phone number, fax number, and e-mail address (if applicable). Specific permission to publish should be cited in the cover letter or appended as a postscript. CHEST reserves the right to edit letters for length and clarity. Readers are also encouraged to view the electronic Letters to the Editor at www.chestjournal.org

Xenobiotic Enzymes and Genetics of COPD

To the Editor:

In a recent issue of *CHEST* (May 2004), Molfino[1] reported that current knowledge of the genetics of COPD is limited. He clearly indicated that the inconsistent results from association studies of candidate genes and COPD may be due to the phenotype definitions used or to ethnic differences among the patients in the studies. That is why some preliminary conclusions can be drawn.

Although he cited many articles on candidate gene-association studies and linkage analyses, which have been reported for COPD patients, the pathogenesis of COPD associated with the xenobiotic enzyme has been totally neglected. It has been suggested that genetic polymorphisms in xenobiotic enzymes may have a role in individual susceptibility to oxidant-related lung disease.[2-4] The first-pass metabolism of foreign compounds in the lung is an important protective mechanism against oxidative stress. The polymorphisms in the genes for cytochrome P450, microsomal epoxide hydrolase (mEPHX) and glutathione S-transferase (GST) P1, which are the enzymes involved in this protective process, had some bearing on individual susceptibility to the development of COPD.[2-4] As shown in Figure 1, xenobiotics are closely associated with the oxidant-antioxidant imbalance, which is one of the two major hypotheses in the pathogenesis of smoke-related COPD. Further, oxidant-antioxidant imbalance causes the oxidative inactivation of antiproteinases, alveolar epithelial injury, increased sequestration of neutrophils in the pulmonary microvasculature, and gene expression of proinflammatory mediators.

Each puff of a cigarette contains 10^{17} free radicals and about 4,000 substrates, including carcinogenic agents and other possible causative agents of COPD such as volatile aldehydes and hydrogen cyanide.[5] Thus, defects in the detoxification of these

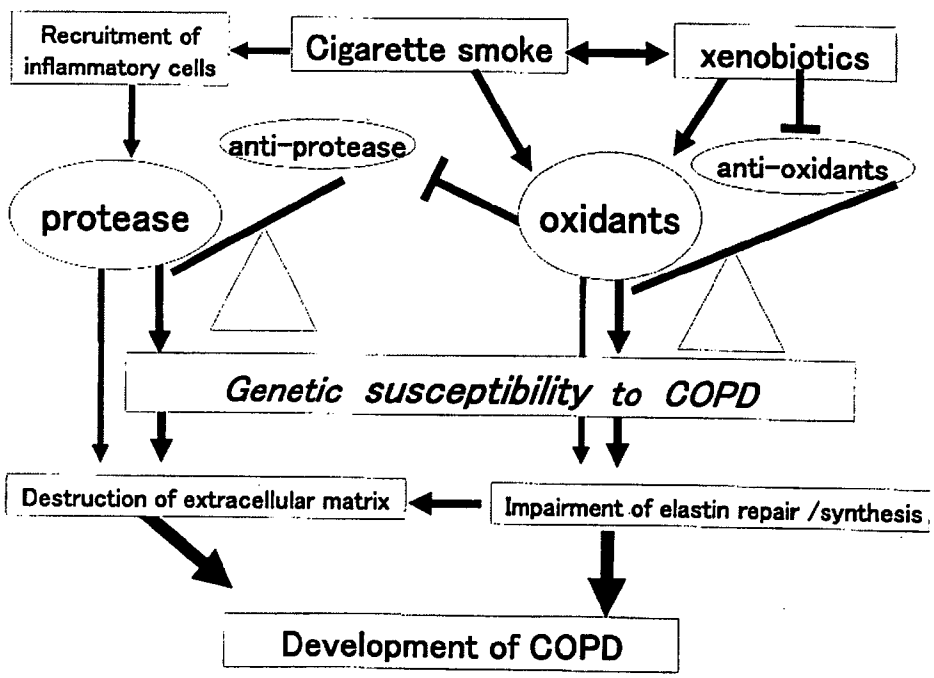

FIGURE 1. Hypothesis of genetic susceptibility to COPD.

reactive species may predispose smokers to airflow obstruction and emphysema. Indeed, mEPHX activity was significantly higher in patients with COPD, when compared to healthy control subjects.[6] These findings have been supported by the study of Sandford and colleagues,[7] who assessed a well-characterized cohort of patients from the Lung Health Study.

We have reported that the genetic polymorphism of exon 5 of smokers with GSTP1 is associated with the development of COPD in smokers.[3] Because the GSTP1/Ile105 genotype is predominantly found in smokers with COPD (72%), but not in smokers without airflow limitation (52%), the GSTP1/Ile105 genotype may be less protective against the xenobiotics in tobacco smoke. Recent data[8] further support the idea that the GSTP1/Ile105 homozygote is associated with an increase in IgE and histamine after challenge with diesel exhaust particles and allergens. Although cigarette smoking is the most important risk factor for the development of COPD, allergic airway inflammation, long-standing asthma, air pollutants, diesel exhaust particles, and xenobiotics also may cause irreversible airflow limitation such as COPD. It has been reported[9] that tunnel workers being exposed to gases and particles from blasting and diesel exhausts are likely to develop COPD. Therefore, subjects exposed to diesel exhaust particles are susceptible to the accelerated decline of lung function, resulting in COPD.

There is growing evidence for the role of xenobiotics and antioxidant imbalance in the pathogenesis of airflow obstruction, which is supported by the results of association studies between COPD and variants in epoxide hydrolase and GSTs that detoxify free radicals and other tobacco products.[10-14] Before these associations are generally accepted, they must be subjected to scrutiny with further association studies in terms of ethnicity and COPD phenotypes.

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To the Editor:

I fully agree with Dr. Teramoto's comments that xenobiotic enzymes seem to play a role in protecting the lung compartment but that their exact role in the pathogenesis of COPD is not clear. This is mentioned in my review[1] (pages 1932 to 1933). Most of the findings described by Dr. Teramoto were also mentioned and referenced in my review.[1]

Nevertheless, I would like to propose to Dr. Teramoto that, despite these findings, genetics may only take us this far. A more complete interpretation of how genes play a role in human lung disease requires a higher level of integration with computational genomics, proteomics, and lung physiology. Thus, isolated findings in one gene or gene family, while helpful in moving the field forward, may not provide a comprehensive answer.[2]

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Inaccurate Spirometry Results?

Let's Blame It on the Computer!

To the Editor:

I read the article by Townsend et al (May 2004)[1] with great interest as well as consternation. Although the authors would have the reader believe that the errors referred to are due to equipment error, based on the examples given, whether or not there is a hardware problem (*eg*, flow-sensor "zero error") or a software problem (*eg*, the inability to delete inaccurate volume-time or flow-volume curves), the individual who is administering

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Significance of chronic cough as a defence mechanism or a symptom in elderly patients with aspiration and aspiration pneumonia

To the Editors:

In a recent issue of the *European Respiratory Journal*, MORICE and the European Respiratory Society (ERS) Task Force committee members [1] comprehensively summarised the diagnosis and management of chronic cough in both adults and children. However, they have totally neglected the features, diagnosis and management of chronic cough in the elderly [1].

Although cough is one of the most common symptoms for which patients seek medical attention from primary care physicians and pulmonologists all over the world and is associated with deterioration in patients' quality of life [1], the concise and distinct guideline is not extensively introduced. Thus, the recent ERS Task Force report "The diagnosis and management of chronic cough" is very helpful and meaningful for chest physicians as well as primary care physicians. However, age-related changes in cough reflex and the protective roles of cough as the defence mechanism of aspiration in older patients are not argued in the report.

PALOMBINI *et al.* [2] reported that asthma, postnasal drip syndrome (PNDS) and gastro-oesophageal reflux disease (GERD), alone or in combination, were responsible for $\geq 90\%$ of the causes of chronic cough. They proposed that asthma, PNDS and GERD should be called a pathological triad in chronic cough in adults [2]. However, in older patients, the causes of chronic cough may be more complicated. Age-related changes in cough reflex may affect the causes and therapeutic efficacy of chronic cough [3]. Furthermore, the protective role of cough as the defence mechanism of aspiration is very important for the pathogenesis of chronic cough in older patients. Owing to the increasing number of the elderly in the population, many pulmonologists and geriatricians recognised that silent aspiration might be very important for the pathogenesis of aspiration pneumonia and nosocomial pneumonia in older patients [4–7]. The prevalence of stroke, chronic obstructive pulmonary disease, sleep apnoea, gastro-oesophageal reflux, sedatives and/or hypnotics usage, post-gastrectomy and mechanical ventilation are increased in the aged population and these are believed to increase the risk of aspiration [4–7]. As pneumonia is in principle prevented by the defence mechanisms, such as upper airway reflexes, mucociliary clearance and phagocytosis by alveolar macrophages, age-dependent declines of upper airway reflexes may be one of the pathophysiological features of aspiration pneumonia in older subjects. Elderly persons appear to have slowed clearance of particles from the airway probably due to impaired mucociliary function that accompanies ageing. However, in our experience, cough reflexes rather than swallowing reflex or mucociliary clearance are of the utmost importance for preventing aspiration in elderly patients. In fact, a markedly decreased cough reflex was observed in elderly patients with aspiration pneumonia [3, 4]. Inversely, there is growing evidence that angiotensin-converting enzyme (ACE) inhibitors have beneficial effects on the prevention of pneumonia in elderly patients by improving both the impaired swallowing reflex and disturbed cough reflex [8, 9]. Although the elevated levels of bradykinin and substance P by ACE inhibitors are thought to be the source of the cough, bradykinin and substance P play a role in setting the threshold for the cough and swallowing reflex in humans, resulting in reduction of the occurrence of pneumonia in the elderly. The beneficial effects of ACE inhibitors for older subjects with the risk of aspiration pneumonia should be widely noted [8, 9].

In addition, we have recently demonstrated that recurrent silent aspiration causes diffuse aspiration bronchiolitis (DAB), which is characterised as a chronic inflammation of bronchioles accompanying a foreign body reaction [3, 10]. The patients with DAB mostly demonstrated signs of bronchorrhoea, cough, bronchospasm and dyspnoea in the case of food intake. The chronic cough in association with food intake is often misdiagnosed as bronchial asthma in the elderly. The chronic cough in DAB does not respond to β-adrenergic bronchodilators or to inhaled steroids. The swallowing rehabilitation and temporally *i.v.* alimentation are the most effective way to reduce the symptoms in DAB.

Although chronic cough is an untoward symptom in adults as well as elderly subjects, the protective roles of cough reflex on the development of aspiration pneumonia in older patients should be carefully considered by all physicians. Hopefully, the next European Respiratory Society Task Force report will include the clinical significance of chronic cough as a defence mechanism or a symptom in elderly patients with aspiration and aspiration pneumonia.

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