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文献泛读


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Mild Chronic Obstructive Pulmonary Disease Does Exist—and Affects Gas Exchange during Exercise

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- ▶ definition of chronic obstructive pulmonary disease (COPD) and how it should be assessed physiologically(生理学方面)
- ▶ The Global Initiative --persistent(固执的) airflow(气流) limitation(限制) objectively(客观地) confirmed(确认) by an FEV_1/FVC ratio(比率) of 0.7 or less (1).
- ▶ Others highlighted(突出) the **age-related decline**(下降) in this ratio and suggested that to avoid overdiagnosing the condition, it should only be diagnosed(诊断) when the ratio was **below the lower limit of normal derived**(源于) from appropriate(适当的) **predictive**(预言性的) equations(方程式) for the population under study
- ▶ COPD is progressive(进步的) over time

- ▶ One way to do this is to stress(强调) the respiratory system by *observing how well gas exchange* is maintained(维持) *during exercise*.
- ▶ *Abnormalities in gas exchange* including significant(重大的) oxygen desaturation(减饱和) appear to be secondary to the deranged lung mechanics in established disease.
- ▶ In contrast, in mild COPD, there is a *widened*(扩展了的) *alveolar-arterial gradient*(梯度) and a preponderance(优势) of low *V.A/Q* lung units.

- ▶ Clearly, patients can develop *modest degrees of exercise limitation* and symptoms(症状) when their *spirometric(肺活量的) abnormalities are relatively trivial*.
 - ▶ Neither resting nor dynamic(动态的) hyperinflation(高度膨胀) were needed for this to be present.
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- ▶ All of this emphasizes(强调) that *important functional*, and hence structural(结构的), *changes* that occur in COPD happen *well before we become aware* of them as clinicians(临床医生).

Molecular Phenotyping. A Guide to Improving Detection of Interstitial Lung Disease in Patients with Rheumatoid Arthritis

- ▶ In two independent cohorts of patients with RA-ILD, the authors tested the associations of age, sex, smoking history, rheumatoid factor, *anticyclic citrullinated peptide antibodies*, *MMP7*, *pulmonary and activation-regulated chemokine*, and *surfactant protein-D* alone and in combination to develop a clinical prediction model to identify RA-ILD.

Do Patients of Subspecialist Physicians Benefit from Written Asthma Action Plans?

- ▶ **Abstract**
- ▶ **Rationale:** *Asthma clinical guidelines* suggest **written asthma action plans** are essential for improving self-management and outcomes.
- ▶ **Objectives:** To assess the *efficacy of written instructions* in the form of a written asthma action plan provided by subspecialist physicians as part of usual asthma care during office visits.
- ▶ **Methods:** A total of *407* children and adults with persistent asthma receiving first-time care in pulmonary and allergy practices at *4 urban medical centers* were **randomized** to receive either written instructions (n = 204) or no written instructions other than prescriptions (n = 203) from physicians.

- ▶ **Measurements and Main Results:** Using written asthma action plan forms as a vehicle for providing self-management instructions *did not have a significant effect* on any of the primary outcomes: (1) asthma symptom frequency, (2) emergency visits, or (3) asthma quality of life from baseline to 12-month follow-up. *Both groups showed similar and significant reductions* in asthma symptom frequency (daytime symptoms [$P < 0.0001$], nocturnal symptoms [$P < 0.0001$], β -agonist use [$P < 0.0001$]). There was also a significant reduction in emergency visits for the intervention ($P < 0.0001$) and control ($P < 0.0006$) groups. There was significant improvement in asthma quality-of-life scores for adults ($P < 0.0001$) and pediatric caregivers ($P < 0.0001$).
- ▶ **Conclusions:** Our results suggest that using a written asthma action plan form as a vehicle for providing asthma management instructions to patients with *persistent asthma* who are receiving subspecialty care *for the first time confers no added benefit* beyond **subspecialty-based medical care** and education for asthma.

Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease. Implications for Dyspnea and Exercise Intolerance

▶ Abstract

- ▶ **Rationale:** Several studies in mild chronic obstructive pulmonary disease (*COPD*) have shown a *higher* than normal *ventilatory equivalent for carbon dioxide* ($V.E/V.CO_2$) during exercise. Our objective was to examine pulmonary gas exchange abnormalities and the *mechanisms of high $V.E/V.CO_2$* in mild COPD and *its impact* on dyspnea and exercise intolerance.
- ▶ **Methods:** Twenty-two subjects (11 patients with GOLD [Global Initiative for Chronic Obstructive Lung Disease] grade 1B COPD, 11 age-matched healthy control subjects) *undertook physiological testing* and a symptom-limited incremental cycle exercise test with arterial blood gas collection.

- ▶ **Measurements and Main Results:** Patients (post-bronchodilator FEV₁: 94 ± 10% predicted; mean ± SD) had evidence of *peripheral airway dysfunction* and *reduced peak oxygen uptake* compared with control subjects (80 ± 18 vs. 113 ± 24% predicted; $P < 0.05$). *Arterial blood gases were within the normal range* and effective alveolar ventilation was not significantly different from control subjects throughout exercise. The *alveolar-arterial O₂ tension gradient was elevated* at rest and throughout exercise in COPD ($P < 0.05$). V.E/V.CO₂, *dead space to tidal volume ratio* (V_D/V_T), and *arterial to end-tidal CO₂ difference* were all higher ($P < 0.05$) in patients with COPD than in control subjects during exercise. In patients with COPD versus control subjects, there was significant dynamic hyperinflation and greater tidal volume constraints ($P < 0.05$). Standardized dyspnea intensity ratings were also higher ($P < 0.05$) in patients with COPD versus control subjects in association with higher ventilatory requirements. Within all subjects, V_D/V_T correlated with the V.E/V.CO₂ ratio during submaximal exercise ($r = 0.780$, $P < 0.001$).
- ▶ **Conclusions:** *High V_D/V_T* was the most consistent gas exchange abnormality in smokers with only mild spirometric abnormalities. Compensatory increases in minute ventilation during exercise maintained alveolar ventilation and arterial blood gas homeostasis but at the expense of earlier dynamic mechanical constraints, greater dyspnea, and exercise intolerance in mild COPD.

Multifaceted Role for IL-17A in the Pathogenesis of Chronic Obstructive Pulmonary Disease



IL-17A Is Elevated in End-Stage Chronic Obstructive Pulmonary Disease and Contributes to Cigarette Smoke-induced Lymphoid Neogenesis

- ▶ **Rationale:** End-stage chronic obstructive pulmonary disease (COPD) is associated with an accumulation of pulmonary lymphoid(淋巴的) follicles(卵泡). IL-17A is implicated in COPD and pulmonary lymphoid neogenesis(新生) in response to microbial(微生物的) stimuli(刺激). We hypothesized(假设) that IL-17A is increased in peripheral lung tissue during end-stage COPD and also directly contributes to cigarette smoke-induced lymphoid neogenesis.
- ▶ **Objectives:** To characterize the *tissue expression* and functional role of IL-17A in *end-stage COPD*.
- ▶ **Methods:** Automated immune *detection* of IL-17A and IL-17F was performed in lung tissue specimens(样品) collected from patients with Global Initiative for Chronic Obstructive Lung Disease stage I-IV COPD, and smoking and never-smoking control subjects. In parallel, *Il17a*^{-/-} mice and wild-type control animals were exposed to cigarette smoke for 24 weeks, and pulmonary lymphoid(淋巴的) neogenesis(新生) was assessed.

- ▶ **Measurements and Main Results:** Tissue expression of IL-17A and IL-17F was *increased in COPD* and correlated(关联) *with lung function decline*. IL-17A was significantly elevated in severe to very severe COPD compared with both smokers and never-smokers without COPD. Although CD3⁺ T cells expressed IL-17A in very severe COPD, most IL-17A⁺ cells were identified as tryptase-positive mast cells. Attenuated(减弱) lymphoid neogenesis and reduced expression of the B-cell attracting chemokine(趋化因子) C-X-C motif ligand(配合基) *(CXCL) 12* was observed in cigarette smoke-exposed *Il17a^{-/-} mice*. CXCL12 was also highly expressed in lymphoid follicles(卵泡) in COPD lungs, and the pulmonary expression was significantly elevated in end-stage COPD.
- ▶ **Conclusions:** IL-17A in the peripheral lung of patients with severe to very severe COPD may contribute to disease progression and development of lymphoid follicles via activation of CXCL12.

The Effect of Macrolide Resistance on the Presentation and Outcome of Patients Hospitalized for *Streptococcus pneumoniae* Pneumonia

- ▶ **Rationale:** There are conflicting reports describing the effect of macrolide resistance on the presentation and outcomes of patients with *Streptococcus pneumoniae* pneumonia.
- ▶ **Objectives:** We aimed to determine the effect of macrolide resistance on the ***presentation and outcomes*** of patients ***with pneumococcal pneumonia***.
- ▶ **Methods:** We conducted a retrospective, observational study in the Hospital Clinic of Barcelona of all adult patients hospitalized with pneumonia who had positive cultures for *S. pneumoniae* from January 1, 2000 to December 31, 2013. ***Outcomes*** examined included bacteremia, pulmonary complications, acute renal failure, shock, intensive care unit admission, need for mechanical ventilation, length of hospital stay, and 30-day mortality.

- ▶ **Measurements and Main Results:** Of 643 patients hospitalized for *S. pneumoniae* pneumonia, 139 (22%) were macrolide resistant. Patients with macrolide-resistant organisms were less likely to have bacteremia, pulmonary complications, and shock, and were less likely to require noninvasive mechanical ventilation. We found *no increase* in the incidence of acute renal failure, the frequency of intensive care unit admission, the need for invasive ventilatory support, the length of hospital stay, or the 30-day mortality in patients with (invasive or noninvasive) macrolide-resistant *S. pneumoniae* pneumonia, and no effect on outcomes as a function of whether treatment regimens did or did not comply with current guidelines.
- ▶ **Conclusions:** We found no evidence suggesting that patients hospitalized for macrolide-resistant *S. pneumoniae* pneumonia were more severely ill on presentation or had worse clinical outcomes if they were treated with guideline-compliant versus noncompliant regimens.

Effect of Ultrafiltration on Sleep Apnea and Sleep Structure in Patients with End-Stage Renal Disease

- ▶ **Rationale:** In end-stage renal disease (ESRD), a condition characterized by fluid overload, both obstructive and central sleep apnea (OSA and CSA) are common. This observation suggests that fluid overload is involved in the pathogenesis of OSA and CSA in this condition.
- ▶ **Objectives:** To test the hypothesis that fluid removal by ultrafiltration (UF) will reduce severity of OSA and CSA in patients with ESRD.
- ▶ **Methods:** At baseline, on a nondialysis day, patients with ESRD on thrice-weekly hemodialysis underwent overnight polysomnography along with measurement of total body extracellular fluid volume (ECFV), and ECFV of the neck, thorax, and right leg before and after sleep. The following week, on a nondialysis day, subjects with an apnea-hypopnea index (AHI) greater than or equal to 20 had fluid removed by UF, followed by repeat overnight polysomnography with fluid measurements.

- ▶ **Measurements and Main Results:** Fifteen patients (10 men) with an AHI greater than or equal to 20 (10 OSA; 5 CSA) participated. Mean age was 53.5 ± 10.4 years and mean body mass index was 25.3 ± 4.8 kg/m². Following removal of 2.17 ± 0.45 L by UF, the AHI decreased by 36% (43.8 ± 20.3 to 28.0 ± 17.7 ; $P < 0.001$) without affecting uremia. The reduction in AHI correlated with the reduction in total body ECFV ($r = 0.567$; $P = 0.027$) and was associated with reductions in ECFV of the right leg ($P = 0.001$), overnight change in ECFV of the right leg ($P = 0.044$), ECFV of the thorax ($P = 0.001$), and ECFV of the neck ($P = 0.003$).
- ▶ **Conclusions:** These findings indicate that fluid overload contributes to the pathogenesis of OSA and CSA in ESRD, and that fluid removal by UF attenuates sleep apnea without altering uremic status.

Targeting 'types: Precision Medicine in Pulmonary Disease

- ▶ **Muscle Weakness in Critical Illness**

Personalizing Medicine. Quantification of Cystic Fibrosis Using Computed Tomography

Noninvasive Analysis of the Sputum Transcriptome Discriminates Clinical Phenotypes of Asthma

- ▶ **Rationale:** The airway transcriptome includes genes that contribute to the pathophysiologic heterogeneity seen in individuals with asthma.
- ▶ **Objectives:** We analyzed *sputum gene expression* for transcriptomic endotypes of asthma (*TEA*), gene signatures that discriminate phenotypes of disease.
- ▶ **Methods:** Gene expression in the sputum and blood of patients with asthma was measured using *Affymetrix microarrays*. Unsupervised clustering analysis based on pathways from the Kyoto Encyclopedia of Genes and Genomes was used to identify *TEA clusters*. Logistic regression *analysis of matched blood samples* defined an expression profile in the circulation to determine the TEA cluster assignment in a cohort of children with asthma to replicate clinical phenotypes.

- ▶ **Measurements and Main Results:** *Three TEA clusters* were identified. TEA cluster 1 had the most subjects with a history of intubation ($P=0.05$), a lower prebronchodilator FEV₁ ($P=0.006$), a higher bronchodilator response ($P=0.03$), and higher exhaled nitric oxide levels ($P=0.04$) compared with the other TEA clusters. TEA cluster 2, the smallest cluster, had the most subjects that were hospitalized for asthma ($P=0.04$). TEA cluster 3, the largest cluster, had normal lung function, low exhaled nitric oxide levels, and lower inhaled steroid requirements. Evaluation of TEA clusters in children confirmed that TEA clusters 1 and 2 are associated with a history of intubation ($P=5.58 \times 10^{-6}$) and hospitalization ($P=0.01$), respectively.
- ▶ **Conclusions:** There are common *patterns of gene expression* in the sputum and blood of children and adults that are associated with near-fatal, severe, and milder asthma.

- ▶ **Diaphragm Muscle Fiber Weakness and Ubiquitin-Proteasome Activation in Critically Ill Patients**

Conclusions: These findings show that diaphragm muscle fibers of critically ill patients display atrophy and severe contractile weakness, and in the diaphragm (隔膜) of critically ill patients the ubiquitin-proteasome pathway is activated. This study provides rationale for the development of treatment strategies that target the contractility of diaphragm fibers to facilitate weaning (脱机) .

Global Epidemiology of Pediatric Severe Sepsis: The Sepsis Prevalence, Outcomes, and Therapies Study

- ▶ **Conclusions:** *Pediatric severe sepsis* remains a burdensome public health problem, with prevalence, morbidity, and mortality rates similar to those reported in critically ill adult populations. International clinical trials targeting children with severe sepsis are warranted.


Revisiting “Good” and “Bad” Cholesterol. The Battle over Flow through Arteries Now Shifts to Flow through Airways

- ▶ In contrast, among atopic patients with asthma, an atherogenic lipid profile was found to correlate with reduced FEV₁. Specifically, serum HDL-C and apoA-I were positively correlated with FEV₁, whereas serum LDL-C, triglycerides, apoB, and apoB/apoA-I ratio were negatively correlated with FEV₁.
- ▶ Positive correlations were found between FEV₁ and HDL particle size, as well as between FEV₁ and concentration of large HDL particles.

Finding the Key to Dialysis Catheter Lock

- ▶ In sum, this rigorously executed, large, randomized clinical trial of ethanol lock of temporary dialysis catheters ***failed to suggest any benefit of ethanol lock***, and supports other studies suggesting that catheter lock solutions that do not contain antimicrobials ***can improve catheter patency***, and therefore function, but are ***not associated*** with decreased risk for ***CRI***.

Nighttime in the Intensive Care Unit. A Lens into the Value of Critical Care Delivery

- ▶ In conclusion, there are undoubtedly some ICU patients who would do better if they were managed by a trained intensivist at night, and by the same intensivist each night, and if they were not discharged until that intensivist thought the timing was optimal, uninfluenced by bed pressures. However, the vast majority of critically ill patients appear to be either too sick or too well to benefit from nighttime intensivist staffing, continuous intensivist coverage, or spending several more hours in the ICU. For this great majority of patients, rather than auditing ICU practices of dubious value, we should instead focus on developing parallel care paradigms in non-ICU settings that could achieve similar outcomes at lower costs. At the same time, it seems prudent to continue examining critical care delivery at night with an eye toward identifying additional aspects of care delivery that add little value.
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The Timing of Discharge from the Intensive Care Unit and Subsequent Mortality. A Prospective, Multicenter Study

- ▶ **Rationale:** Previous studies suggested an association between after-hours intensive care unit (ICU) discharge and increased hospital mortality. Their *retrospective design* and lack of correction for patient *factors present at the time of discharge* make this association problematic.
- ▶ **Objectives:** To determine factors independently associated with mortality after ICU discharge.
- ▶ **Methods:** This was a prospective, multicenter, binational observational study involving 40 ICUs in Australia and New Zealand. Participants were consecutive adult patients discharged alive from the ICU between September 2009 and February 2010.

- ▶ **Measurements and Main Results:** We studied 10,211 patients discharged alive from the ICU. Median age was 63 years (interquartile range, 49–74), 6,224 (61%) were male, 5,707 (56%) required mechanical ventilation, and their median Acute Physiology and Chronic Health Evaluation III risk of death was 9% (interquartile range, 3–25%). A total of 8,539 (83.6%) patients were discharged in-hours (06:00–18:00) and 1,672 (16.4%) after-hours (18:00–06:00). Of these, 408 (4.8%) and 124 (7.4%), respectively, subsequently died in hospital ($P < 0.001$). After risk adjustment for markers of illness severity at time of ICU discharge including limitations of medical therapy (*LOMT*) orders, the time of discharge was no longer a significant predictor of mortality. The presence of a LOMT order was the strongest predictor of death (odds ratio, 35.4; 95% confidence interval, 27.5–45.6).
- ▶ **Conclusions:** In this large, prospective, multicenter, binational observational study, we found that *patient status at ICU discharge*, particularly *the presence of LOMT orders*, was the chief predictor of hospital survival. In contrast to previous studies, the timing of discharge did not have an independent association with mortality.

Ethanol Lock and Risk of Hemodialysis Catheter Infection in Critically Ill Patients. A Randomized Controlled Trial

- ▶ **Rationale:** Ethanol rapidly eradicated experimental biofilm(细菌膜). Clinical studies of ethanol lock to prevent catheter-related infections (CRIs) suggest preventive efficacy. No such studies have been done in intensive care units (ICU).
- ▶ **Objectives:** To determine whether ethanol lock decreases the risk of major CRI in patients with short-term dialysis catheters (*DCs*).
- ▶ **Methods:** A randomized, double-blind, placebo-controlled trial was performed in 16 ICUs in seven university hospitals and one general hospital in France between June 2009 and December 2011. Adults with insertion of a nontunneled, nonantimicrobial-impregnated double-lumen DC for an expected duration greater than 48 hours, to perform renal-replacement therapy or plasma exchange, were randomly allocated (1:1) to receive a 2-minute catheter lock with either 60% wt/wt ethanol solution (ethanol group) or 0.9% saline solution (control group) at the end of DC insertion and after each renal-replacement therapy or plasma exchange session. The main outcome was major CRI defined as either catheter-related clinical sepsis without bloodstream infection or catheter-related bloodstream infection during the ICU stay.

- ▶ **Measurements and Main Results:** The intent-to-treat analysis included 1,460 patients (2,172 catheters, 12,944 catheter-days, and 8,442 study locks). Median DC duration was 4 days (interquartile range, 2–8) and was similar in both groups. Major CRI incidence did not differ between the ethanol and control groups (3.83 vs. 2.64 per 1,000 catheter-days, respectively; hazard ratio, 1.55; 95% confidence interval, 0.83–2.87; $P=0.17$). No significant differences occurred for catheter colonization ($P=0.57$) or catheter-related bloodstream infection ($P=0.99$).
- ▶ **Conclusions:** A 2-minute ethanol lock does not decrease the frequency of infection of DCs in ICU patients.