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The APSR Research Update Series for Pulmonary Circulation.

In this issue, I have selected and discussed briefly the excellent and important 10 articles as follows published in the last year on a topic of Pulmonary Circulation Area.

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Strategic plan for lung vascular research: An NHLBI-ORDR Workshop Report.

Authors: Erzurum S *et al.*

Reference: Am J Respir Crit Care Med. 2010; 182:1554-62.

URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3029941/?tool=pubmed>

Comments: This NHLBI-ORDR (National Heart, Lung, and Blood Institute, with the Office of Rare Diseases Research) Workshop Report has identified the priority areas and strategic goals to enhance and accelerate researches in the care of patients with pulmonary vascular diseases. The focus for future research efforts include the following : (1) better characterizing vascular genotype-phenotype relationships and incorporating systems biology approaches when appropriate; (2) advancing our understanding of pulmonary vascular metabolic regulatory signaling in health and disease; (3) expanding our knowledge of the biological relationships between the lung circulation and circulating elements, systemic vascular function, and right heart function and disease; (4) improving translational research for identifying disease-modifying therapies for the pulmonary hypertensive diseases; (5) establishing an appropriate and effective platform for advancing translational findings into clinical studies testing; and (6) developing the specific technologies and tools that will be enabling for these goals, such as question-guided imaging techniques and lung vascular investigator training programs.

The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation.

Authors: Villar J *et al.*

Reference: Intensive Care Med. 2011; 37:1932-41.

URL: <http://www.springerlink.com/content/e48u7273816v3tr1/?MUD=MP>

Comments: The ALIEN (Acute Lung Injury : Epidemiology and Natural history) Network performed this 1-year prospective, multicenter, observational study in 13 geographical areas of Spain in order to examine acute respiratory distress syndrome (ARDS) incidence and outcome under current lung protective ventilatory support practices before and after the diagnosis of ARDS. A total of 255 mechanically ventilated patients fulfilled the ARDS definition, and represented an incidence of 7.2/100,000 population/year. Pneumonia and sepsis were the most common causes of ARDS. At the time of meeting ARDS criteria, mean PaO₂/FiO₂ was 114 ± 40 mmHg, mean tidal volume was 7.2 ± 1.1 ml/kg predicted body weight, mean plateau pressure was 26 ± 5 cmH₂O, and mean positive end-expiratory pressure (PEEP) was 9.3 ± 2.4 cmH₂O. Overall ARDS ICU and hospital mortality was 42.7% (95%CI 37.7-47.8) and 47.8% (95%CI 42.8-53.0), respectively. The authors have concluded that despite use of lung protective ventilation, overall ICU and hospital mortality of ARDS patients is still higher than 40%.

Cell-based therapies for lung vascular diseases: lessons for the future.

Authors: Stewart DJ, Mei SH.

Reference: Proc Am Thorac Soc. 2011; 8:535-40.

URL: <http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%2022052933>

Comments: Pulmonary arterial hypertension (PAH) or acute respiratory distress syndrome (ARDS) represents diseases caused in large part by lung endothelial injury and inflammation. This review article focuses the possibilities of cellular therapies to PAH and ARDS in the future. The therapies include the delivery of *ex-vivo* transfected somatic cells to the pulmonary circulation and the combination of progenitor cells with the overexpression of the therapeutic transgenes.

Neuromuscular blockers in early acute respiratory distress syndrome.

Authors: Papazian L *et al.*

Reference: N Engl J Med. 2010; 363:1107-16.

URL: <http://www.nejm.org/doi/full/10.1056/NEJMoa1005372>

Comments: The ACURASYS (ARDS et Curarisation Systematique) study performed this multicenter, double-blind trial in order to evaluate clinical outcomes after 2 days of therapy with neuromuscular blocking agents of either cisatracurium besylate (178 patients) or placebo (162 patients) in 340 patients with early, severe acute respiratory distress syndrome (ARDS). Severe ARDS was defined as PaO₂/FiO₂ of less than 150, with a positive end-expiratory pressure of 5 cm or more of water and a tidal volume of 6 to 8 ml per kilogram of predicted body weight. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (P=0.08). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (P=0.05). The rate of ICU-acquired paresis did not differ significantly between the two groups. The authors have concluded that early administration of a neuromuscular blocking agent improves the adjusted 90-day survival and increases the time off the ventilator without increasing muscle weakness in patients with severe ARDS.

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Vardenafil in pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled study.

Authors: Jing ZC *et al.*

Reference: Am J Respir Crit Care Med. 2011; 183:1723-9.

URL: <http://ajrccm.atsjournals.org/content/183/12/1723.long>

Comments: This randomized, double-blind, placebo-controlled study tried to evaluate the safety and efficacy of vardenafil, a new phosphodiesterase type 5 inhibitor, in Chinese patients with pulmonary arterial hypertension (PAH). Sixty-six patients with PAH were randomized 2:1 to vardenafil (5 mg once daily for 4 wk then 5 mg twice daily; n = 44) or placebo (n = 22) groups for 12 weeks. Vardenafil, when compared with placebo, increased 6-minute walking distance (69m; $p < 0.001$) and cardiac index ($0.39 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$; $P = 0.005$), and decreased mean pulmonary artery pressure and pulmonary vascular resistance (-5.3 mm Hg , $P = 0.047$; -4.7 Wood U , $P = 0.003$; respectively) at Week 12. Vardenafil was associated with only mild and transient adverse events. Thus, vardenafil is effective and well tolerated in patients with PAH at a dose of 5 mg twice daily.

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Leptin promotes fibroproliferative acute respiratory distress syndrome by inhibiting peroxisome proliferator-activated receptor- γ .

Authors: Jain M *et al.*

Reference: Am J Respir Crit Care Med. 2011; 183:1490-8.

URL: <http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%2021317313%20>

Comments: Although leptin, a 16-KD non-glycosylated protein, is classically considered to regulate the balance food intake and energy expenditure, it is a member of the type I cytokine family. On the other hand, the patients with diabetes mellitus have had a lower incidence and better prognosis of acute respiratory distress syndrome (ARDS). Because type II diabetic patients are associated with hyperleptinemia and an acquired resistance to signaling through the leptin receptor, leptin may play a role in the pathogenesis of ARDS. This study was tried to determine whether leptin resistance, a feature of diabetes, prevents fibro-proliferation after lung injury. The authors examined lung injury and fibro-proliferation after the intratracheal instillation of bleomycin in wild-type and leptin-resistant (db/db) diabetic mice, and furthermore the effect of leptin on transforming growth factor (TGF- β ₁)-mediated transcription in primary normal human lung fibroblasts. They also measured leptin and active TGF- β ₁ levels in bronchoalveolar lavage fluid (BALF) from patients with ARDS and ventilated control subjects. The main results were as follows; Diabetic mice (db/db) were resistant to lung fibrosis. The db/db mice had higher levels of peroxisome proliferator-activated receptor- γ (PPAR γ), an inhibitor of the transcriptional response to TGF- β ₁, a cytokine critical in the pathogenesis of fibroproliferative ARDS. In normal human lung fibroblasts, leptin augmented the transcription of profibrotic genes in response to TGF- β ₁ through a mechanism that required PPAR γ . In patients with ARDS, leptin levels in BALF were elevated and correlated with TGF- β ₁ levels. Overall, there was no significant relationship between BALF leptin levels and clinical outcomes; however, in non-obese patients, higher BALF leptin levels were associated with fewer intensive care unit- and ventilator-free days and higher mortality. Thus, leptin signaling is required for bleomycin-induced lung fibrosis. Leptin augments TGF- β ₁ signaling in lung fibroblasts by inhibiting PPAR γ . These findings provide a mechanism for the observed protection against ARDS observed in diabetic patients.

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Functional disability 5 years after acute respiratory distress syndrome.

Authors: Herridge MS *et al.*

Reference: N Engl J Med. 2011; 364:1293-304.

URL: <http://www.nejm.org/doi/full/10.1056/NEJMoa1011802>

Comments: Because there have been few detailed data about the long-term outcome among survivors of the acute respiratory distress syndrome (ARDS), the Canadian Critical Care Trials Group evaluated 109 survivors of ARDS at 3, 6, and 12 months and at 2, 3, 4, and 5 years after discharge from the intensive care unit. At each visit, patients were interviewed and examined; underwent pulmonary-function tests, the 6-minute walk test, resting and exercise oximetry, chest imaging, and a quality-of-life evaluation. At 5 years, the median 6-minute walk distance was 436 m (76% of predicted distance) and the Physical Component Score on the Medical Outcomes Study 36-Item Short-Form Health Survey was 41 (mean norm score matched for age and sex, 50). With respect to this score, younger patients had a greater rate of recovery than older patients, but neither group returned to normal predicted levels of physical function at 5 years. Pulmonary function was normal to near-normal. A constellation of other physical and psychological problems developed or persisted in patients and family caregivers for up to 5 years. Patients with more coexisting illnesses incurred greater 5-year costs. Thus, in severe lung injury there are important legacies of exercise limitation, physical and psychological sequelae, decreased physical quality of life, and increased costs and use of health care services.

KL-6 concentration in pulmonary epithelial lining fluid is a useful prognostic indicator in patients with acute respiratory distress syndrome.

Authors: Kondo T *et al.*

Reference: Respir Res. 2011;12: 32.

URL: <http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%2021418654>

Comments: KL-6, a mucin-like glycoprotein expressed on the surface of alveolar type II cells, is elevated in serum and epithelial lining fluid (ELF) in patients with acute respiratory distress syndrome (ARDS). However, kinetics and prognostic significance of KL-6 have not been extensively studied. To clarify these points, 32 ARDS patients who received mechanical ventilation under intubation were studied for 28 days and their KL-levels in serum and epithelial lining fluid (ELF) were examined. ELF was collected using a bronchoscopic micro-sampling procedure. KL-6 levels in ELF on days 0 to 3 after ARDS diagnosis were significantly higher in non-survivors than in survivors, and thereafter, there was no difference in concentrations between the two groups. However, serum KL-6 levels did not show statistically significant differences between non-survivors and survivors at any time point. Patients with KL-6 concentrations in ELF higher than 3,453 U/mL or serum concentrations higher than 530 U/mL had significantly lower survival rates up to 90 days after ARDS diagnosis. The authors have concluded that ELF and serum KL-6 concentrations were found to be good indicators of clinical outcome in ARDS patients, and particularly, KL-6 levels in ELF measured during the early period after the diagnosis were useful for predicting prognosis in ARDS patients

Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome.

Authors: Cottin V *et al.*

Reference: Eur Respir J. 2010; 35:105-11.

URL: <http://erj.ersjournals.com/content/35/1/105.long>

Comments: The combined pulmonary fibrosis and emphysema (CPFE) has been recently individualized which clinically characterizes unique features such as severe dyspnea on exertion, upper-lobe emphysema, lower-lobe fibrosis, subnormal spirometry and severe impairment of gas exchanges. The CPFE syndrome is frequently complicated by pulmonary hypertension (PH), acute lung injury and lung cancer. This clinically retrospective multicentre study was performed to describe the haemodynamic and survival characteristics of 40 patients with PH in CPFE. PaO₂ under room air, mean pulmonary artery pressure, cardiac index (CI) and pulmonary vascular resistance (PVR) were, respectively, 56 ± 12 mmHg, 40 ± 9 mmHg, 2.5 ± 0.7 L x min⁻¹ x m⁻² and 521 ± 205 dyn x s x cm⁻⁵. 1-yr survival was 60%. Higher PVR, higher heart rate, lower CI and lower DLco were associated with shorter survival. Patients with CPFE and PH confirmed by right heart catheterisation have a dismal prognosis despite moderately altered lung volumes and flows and moderately severe haemodynamic parameters

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Treatment of pulmonary arterial hypertension with targeted therapies.

Authors: O'Callaghan DS *et al.*

Reference: Nat Rev Cardiol. 2011; 8:526-38.

URL: <http://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A%2021769113%20>

Comments: This review article shows us the new and investigative therapies for pulmonary arterial hypertension. The therapies are under the phase II and III clinical trials since the 2009 ERS/ESC guidelines (Eur Respir J 2009; 34: 1219-63). The agents include treprostinil (prostanoid), selexipag (prostacyclin receptor agonist), macitentan (tissue targeting ERA (endothelin receptor antagonist)), riociguat (soluble guanylate cyclase stimulator), aviptadil (vaspintestinal peptide oathway), imatinib (tyrosine kinase inhibitor), and simvastain (HMG Co-A(hydroxyl-3- methyl-glutaryl coenzyme A) reductase inhibitor).

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