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Inside this issue: Fukuchi Award and Young Investigator Award Abstracts

In this issue, just after the APSR 2013 Congress in Yokohama, I would like to present to APSR members these Award-winning abstracts again. These are the abstracts selected not only for their impact and scientific significance, but also on the merit and achievements of Young Investigators from different sister societies including ATS, ERS, TSANZ and JRS. Congratulations to the Fukuchi Award recipient Dr Gurgun and also to all the Young Investigators for their pieces of work well done and well deserved their prestigious APSR Awards.

David CL Lam

Department of Medicine, University of Hong Kong.

Fukuchi Award for the Best Paper in Respirology 2013

Effects of nutritional supplementation combined with conventional pulmonary rehabilitation in muscle-wasted chronic obstructive pulmonary disease: A prospective, randomized and controlled study

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ABSTRACT

Background and objective: Nutritional depletion in chronic obstructive pulmonary disease (COPD) adversely affects health status and mortality. We aimed to evaluate the effects of nutritional supplementation (NS) with pulmonary rehabilitation (PR) on body composition, mid-thigh cross-sectional area (CSA), dyspnea, exercise capacity, health-related quality of life, anxiety and depression in advanced COPD patients.

Methods: Forty-six patients were randomized to PR and nutritional support (PRNS), PR or the control group. Dyspnoea was measured with Medical Research Council and BORG scales. Exercise capacity was measured through 6-min walk test and shuttle tests; health related quality of life was assessed with St. George's Respiratory Questionnaire. Psychological status was measured with Hospital Anxiety and Depression Scale. Body weight and body mass indexes (BMI) were also evaluated. Fat-free mass was measured through bioelectrical impedance analyser. The CSA of quadriceps was calculated in mid-level of the thigh with magnetic resonance imaging.

Results: Dyspnoea and total scores of St. George's Respiratory Questionnaire improved in both groups ($P < 0.05$). Six-minute walk test and incremental shuttle walk test distances in PRNS and PR patients increased significantly as (62.6 ± 42.4 m, 43.3 ± 59.2 m, both $P = 0.001$; and 63.3 ± 70.1 m and 69.3 ± 69.7 m, both $P = 0.001$). Although anxiety improved in both groups ($P < 0.05$), there was no change in depression. Body weight, BMI and fat-free mass index (FFMI) (1.1 ± 0.9 kg, 0.2 ± 1.4 kg/m2 and 0.6 ± 0.5 kg/m2, $P < 0.05$) in PRNS, whereas body weight and FFMI (0.6 ± 0.7 kg, 0.1 ± 0.6 kg/m2, $P < 0.05$) increased in PR after the intervention. There was a significant increase in mid-thigh CSA (2.5 ± 4.1 cm2) only in PRNS.

Comments: This was a well conducted randomized controlled clinical trial on the effects of nutritional supplementation combined with pulmonary rehabilitation. The trial results demonstrated nicely the significant improvement of respiratory symptoms, functional state as well as objective nutritional parameters and BMI after implementation a well-planned pulmonary rehabilitation strategy with attention to the nutritional support to the recruited subjects.

YI1 (APSR Young Investigator)

Knockdown of zinc finger E-box binding homeobox 1 (Zeb1) reduced stem cells characteristics of gefitinib-resistant-persisters of PC9 cells

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ABSTRACT:

Background: Acquired resistance to targeted therapy, such as gefitinib, is major problem in EGFR-mutant non-small cell lung cancer (NSCLC). Evidences suggest that cancer stem cells (CSCs) are involved in the resistance of cancer cells to therapy. Zinc finger E-box binding homeobox 1 (ZEB1) is an epithelial-mesenchymal transition inducer that has been linked with stemness maintenance. However, the role of ZEB1 in the maintenance of gefitinib-resistant lung CSC has not been fully understood.

Aim of study: To investigate the role of ZEB1 in CSCs phenotype of gefitinib-resistant-persisters (GRPs)-PC9 cells.

Methods: We exposed PC9 cells to 2 μM of gefitinib for 9 days to obtain GRPs. Quantitative-PCR was conducted to analyze stem cell factors and sphere formation assay was performed to examine the self-renewal of these PC9-GRPs. We knockdown ZEB1 using short-hairpin RNA to obtained stable ZEB1-low expressing PC9 to see the effect on CSCs features of PC9-GRPs.

Results: PC9-GRPs expressed high stem cell factors and could form more sphere numbers as compare to parental PC9. Knockdown of ZEB1 reduced stem cell factors expression in PC9-GRPs as well as reduced sphere numbers. Conclusions: ZEB1 is required to maintain the CSC features of PC9-GRPs, and knockdown of ZEB1 reduced CSC characteristics. Our results suggest that ZEB1 might be potential target to reverse gefitinib resistance in NSCLC.

Comment: This is a simple mechanistic study on a gefitinib resistant lung cancer cell line PC9 addressing a very important scientific as well as clinical question of drug resistance to targeted therapy in EGFR mutant lung cancer that initially responded to targeted therapy.

Find all the abstracts from the 18th APSR congress in :

Respirology Volume 18, Supplement S4

YI2 (APSR Young Investigator)

Clinical and laboratory profiles and outcomes of critically ill chest disease patients in a tertiary care chest hospital

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ABSTRACT:

Background: Critical care in respiratory field has been introduced recently in Bangladesh. Last year a total of 429 patients were admitted in ICU. This prospective observational study was conducted to observe presenting profiles and outcomes of treatment of critically ill chest disease patients.

Methods: All ICU admitted patients were enrolled consecutively. Baseline demographic and laboratory characteristics including primary diagnosis, present clinical problem, arterial blood gas, electrolytes, sputum microscopic findings were noted. Types of intervention and outcomes of the patients in term of death, referral, discharged were noted.

Results: A total of 429 patients were enrolled. Male: Female was 1.66:1. 294 cases (68.5%) had type-2 respiratory failure, mainly due to COPD (74.8%) followed by bilateral bronchiectasis (17.34%), and severe persistent asthma (7.24%). Type-1 respiratory failure was seen in 105 cases (24.4%); due to acute asthma in 42.6%, ARDS in 24.8%, ILD in 32% cases. Mean PCO2 was 76 mm of Hg; range 60-158 mm of Hg. BiPAP was given in all patients. 88.75% was compliant and 72.58% had satisfactory improvement. Invasive ventilation was given to rest. No growth was seen in 46.86% patients on sputum or tracheal aspirates culture. Acinetobacter (36.8%) and pseudomonas (52.4%) were main culprit organisms. Acinetobacter was resistant to all antibiotics except colistin (88.5%). Mortality was 32.4%, 12.87% were referred to other hospitals and 55.6% discharged. Among intubated patients, ventilation associated pneumonia (VAP) followed by septic shock was seen in 64.7% and cardiac arrest due to arrhythmias or myocardial ischemia was seen in 32.9% patients as cause of death.

Conclusion: Type-2 Respiratory failure was the main cause of referral to ICU in this specialized chest hospital. BiPAP was very effective to reduce PCO2. VAP was the predominant cause of death in intubated patients.

Comments: This paper presented well the situation faced with by a newly established intensive care unit in the regional settings. It demonstrated the burden of lung disease caused by COPD with respiratory failure yet fantastic that non-invasive mode of ventilation is available there to support intensive care service to improve morbidity and mortality as a result of invasive ventilation, ultimately with improvement in outcome and health quality service in a regional hospital.

YI3 (ATS Young Investigator)

Healthcare utilization associated with misdiagnosis of COPD in primary care

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ABSTRACT:

Rationale: A diagnosis of chronic obstructive pulmonary disease (COPD) is suggested after history and physical examination and is confirmed by the presence of irreversible airflow obstruction with spirometry. Previous studies have shown problems with both under-diagnosis and over-diagnosis of COPD even in the presence of spirometry. The primary objective of this analysis was to determine if misdiagnosis of COPD was associated with differences in healthcare utilization compared to those accurately diagnosed based on spirometry.

Methods: A cohort of patients at risk for COPD who met the following criteria was included: ≥35 years old; ≥2 primary care visits in internal medicine clinic in 2007; had spirometry performed, and at least one respiratory or smoking cessation medication or diagnosis of COPD within the same year. Using lower limit of normal criteria, the following three groups were defined: 1) presence of COPD diagnosis and obstruction on spirometry (true diagnosis-Group 1), 2) COPD diagnosis with normal spirometry (over-diagnosis-Group 2), and 3) obstruction on spirometry without COPD diagnosis (under-diagnosis-Group 3). Medical records were reviewed 18 months past the inclusion date. Data on all-cause and respiratory-related hospitalizations, emergency department (ED) visits, and ancillary tests were extracted. Odds ratios were determined using logistic regression comparing Group 1 to Group 2 and then Group 3. Variables considered statistically significant in unadjusted comparisons were included in multivariate analyses.

Results: Out of 527 patients identified in the cohort, 103 patients were classified as Group 1, 63 patients as Group 2 and 52 patients as Group 3. In adjusted analysis for Groups 1 and 2, patients who were over-diagnosed were more likely to have at least one all-cause hospitalization (AOR 2.04 [95% CI 1.02-4.04]) and/or ED visit (AOR 2.16 [1.05-4.43]) compared to those with an accurate diagnosis. Patients who were over-diagnosed were more likely to have had a chest radiograph (AOR 2.47 [1.10-5.54]), Chest CT (AOR 2.33 [1.18-4.58]), cardiac catheterization (AOR 2.57 [1.23-5.37]), and/or cardiac stress test (AOR 2.28 [1.06-4.91]) compared to those with a true diagnosis. The adjusted analysis between Groups 1 and 3 did not show any statistically significant differences in health care visits or ancillary tests.

Conclusion: Discrepancies exist between the results of spirometry testing and the diagnosis of patients with COPD in primary care. Our study shows that over-diagnosis of COPD is associated with more all-cause hospitalizations and ED visits and also more respiratory and cardiac ancillary testing.

Comments: This paper addressed another important issue of ‘mis-diagnosis’ of COPD in a big community cohort, identifying the prevalence of ‘over-diagnosis’ as well as ‘under-diagnosis’ of COPD in the primary care setting. This paper brought out the important message to both respir-

atory medicine specialist as well as non-specialist that the correct diagnosis of COPD as well as classification of severity by spirometry is of paramount significance in terms of health care cost and utilization, and the outcome of COPD subjects. Spirometry should be promoted in subjects with clinical suspicion or diagnosis of COPD.

YI4 (ATS Young Investigator)

PET imaging with [11C]PBR28 and [18F]FDG distinguishes macrophage from neutrophil lung inflammation

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ABSTRACT:

Introduction: Noninvasive methods for quantifying macrophage and neutrophil activation and recruitment in chronic obstructive pulmonary disease (COPD) would be highly useful in assessing the efficacy of anti-inflammatory therapies.

Objective: To test whether positron emission tomography (PET) imaging with [^{11}C]PBR28 and [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) could distinguish macrophage-dominant from neutrophilic inflammation in a mouse model of COPD.

Methods: C57BL/6J mice inoculated with PBS or Sendai virus were imaged by microPET (Inveon or Focus 220, Siemens/CTI) with both [^{11}C]PBR28 and [^{18}F]FDG at Days 3 and 84 post-inoculation (p.i.). Regions of interest placed over the lungs determined the % injected dose per cc (%ID/cc) at 60 min. Lung sections were stained for TSPO ([^{11}C]PBR28 ligand), Ly6G (neutrophil marker) and CD68 (macrophage marker).

Results: Only [^{18}F]FDG uptake increased significantly during acute illness at p.i. Day 3. Both [^{11}C]PBR28 and [^{18}F]FDG uptake increased significantly during chronic disease at p.i. Day 84. The [^{11}C]PBR28:[^{18}F]FDG ratio, calculated for each mouse, was no different between infected (1.9±0.3) and uninfected mice (2.0±0.4) at p.i. Day 3. This ratio increased significantly at p.i. Day 84 (3.1±0.9) in infected mice compared to controls (1.7±0.5). Lung sections showed macrophages with intense TSPO staining at p.i. Day 84.

Conclusion: PET imaging with [^{11}C]PBR28 and [^{18}F]FDG quantitatively distinguishes macrophage-dominant from neutrophilic inflammation in a mouse model of COPD. This approach may be useful for monitoring the pulmonary macrophage burden in humans with COPD, thereby guiding emerging targeted anti-inflammatory therapies.

Comments: Relative non-invasive imaging with PET would be a great tool for localizing the site of inflammatory update. It would be even better if the various inflammatory components of macrophage vs. neutrophil activation could be distinguished, especially the latter which has been shown to play an important role in maintenance of protease/anti-protease balance in emphyse-

ma subjects and thus of importance in the pathogenesis, not only in airway inflammation, but pathogenesis of COPD and emphysema.

YI5 (ERS Young Investigators)

Study of incidence, outcome and antibiotic sensitivity pattern of ventilator associated pneumonia in ICU of tertiary care hospital in Nepal

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ABSTRACT:

Background: Ventilator Associated pneumonia (VAP) is an important intensive care unit (ICU)-acquired infection in mechanically ventilated patients. Early and correct diagnosis of VAP is difficult but is an urgent challenge for an optimal antibiotic treatment.

Aim of study: To evaluate the incidence, microbiology and antibiotic sensitivity pattern of Ventilator Associated Pneumonia.

Methods: A prospective, open, epidemiological clinical study was performed in ICU of TUTH, Maharajgunj. 100 patients admitted to ICU and Mechanically Ventilated were evaluated with regard to VAP. Clinical Pulmonary Infection Score (CPIS) was used as tools to diagnose VAP.

Results: Among 60 long-term ventilated patients, 25 (41.6%) developed VAP. The incidence was 25 VAPs per 100 ventilated patients or 26 VAPs per 1000 ventilator days during the period of study. Days on ventilator and duration in ICU were higher in the VAP group. There was a trend towards increasing mortality in the VAP group (p value 0.06). The VAP was caused predominantly by Klebsiella pneumonia in 34.5% of cases, followed by Acinetobacter calcoaceticus baumanni in 27.6%, Acinetobacter wolffi and Pseudomonas aeruginosa in 13.8% each and Escheresia coli in 10.3%. The most sensitive antibiotics were Colistin, followed by Polymyxin B and Amikacin with sensitivity rates of 67%, 60% and 58% respectively.

Conclusion: There exists a high rate of VAP in our ICU. Targeted strategies aimed at reducing VAP should be implemented to improve patient outcome and reduce length of ICU stay and costs.

Comments: In the indexed unit as reported in this paper, VAP was diagnosed in one-fourth of the recruited subjects under surveillance on longer term mechanical ventilation. The results as reported gave reference for future management of VAP in the region and also supported the continue surveillance of antibiotic resistant organisms in the intensive care settings.

YI6 (ERS Young Investigator)

Human Rhinovirus infection of asthmatic airway epithelial cells causes tight junction disassembly resulting in increased permeability.

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ABSTRACT:

Introduction: Human rhinovirus (HRV) has been identified as a major contributor of asthma exacerbations in children and has been suggested to occur by epithelial tight junction (TJ) protein modification and barrier integrity disruption. This study aimed to directly correlate live viral infection with TJ disassembly and whether this leads to barrier compromisation.

Methods: Polarised human epithelial colorectal adenocarcinoma cells (Caco-2), modified human airway epithelial cell (NuLi-1) and primary human airway epithelial cells (pAECs) were infected with HRV-1B at various multiplicity of infection (MOI) over 24 hours. HRV receptor and viral replication were assessed via qPCR while cell viability and apoptosis was assessed via proliferation and apoptotic assays. TJ protein expression of occludin, claudin-1 and zonal occludin-1 (ZO-1) was assessed using in-cell western assays. Transepithelial permeability assays were performed to assess effects on barrier integrity.

Results: Elevated basal LDL receptor expression was observed in asthmatic pAECs compared to healthy, but no significant change was seen in both cohorts following HRV-1B infection. Interestingly, viral replication was significantly higher in asthmatic pAECs compared to the healthy. A MOI-dependent effect on cell viability was observed in both healthy and asthmatic pAECs. Despite a significant 400-fold increase in apoptosis, no significant difference was detected in the apoptotic response between healthy and asthmatic pAECs 24h post infection. Although disassembly of tight junctions occurred with increasing MOI in the pAECs, a greater effect occurred within the asthmatic cohorts. A marked increase in transepithelial permeability was concurrent with this disassembly following infection.

Conclusion: Primary airway epithelial cells more susceptible to HRV-1B infection. At lower MOI, this causes a disassembly of TJ proteins, especially exaggerated in the asthmatic pAECs that is concomitant with increased transepithelial permeability. This may facilitate trafficking of small sized aeroallergens into the sub-epithelial space which could lead to the initiation of asthma exacerbation.

Comments: By means of a couple of human airway epithelial cell models, this mechanistic study demonstrated how the infection of an HRV-prone cell lines will respond to HRV infection with demolition of intercellular bridging protein. This would give insight as to the way aeroallergen penetration may be facilitated to pave the way for subsequent asthma exacerbation in childhood asthmatic subjects.

YI7 (JRS Young Investigator)

One year changes of pulmonary artery pressure in interstitial lung disease

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ABSTRACT:

Background and Aim of Study: Pulmonary hypertension (PH) may complicate the course of interstitial lung disease (ILD) and potentially impact prognosis. Because interval changes in mean pulmonary artery pressures (mPAP) have not fully been studied until now, we sought to evaluate one-year changes of PAP in ILD.

Methods: We retrospectively reviewed ILD patients who underwent right cardiac catheterization (RCC) both at initial evaluation and at one-year after initial evaluation in Tosei General Hospital from May 2007 to March 2012. Patients treated with pulmonary vasodilators or with pulmonary capillary wedge pressure＞14 mmHg were excluded. The prevalence of PH, and the relationships between changes of mPAP and changes of pulmonary functions and exercise capacity were studied. Definition of PH was mPAP＞25 mmHg.

Results: Sixty-one patients with diagnosis of chronic fibrotic pneumonia (idiopathic pulmonary fibrosis in 35, others in 26) were studied. The mean age was 65.3±9.5 years, and 67.2% of the subjects were men. The mean forced vital capacity (FVC) % predicted, diffusing capacity of the lung for carbon monoxide (DLco) % predicted were 76.5±22.4%, 45.8±17.4%, respectively. Thirty-two patients (52.5%) underwent surgical lung biopsy. The follow-up mPAP was significantly higher than initial mPAP (20.1 mmHg vs 17.9 mmHg, p＜0.001), and more patients complicated PH (4.9% vs 16.4%, p=0.075). Changes of mPAP significantly correlated with changes of FVC, DLco, and 6MWT distance (R=0.266, R=0.277, R=0.321, respectively).

Conclusion: In one-year prevalence of PH was higher in patients with ILD. Changes of mPAP correlated with changes in pulmonary functions and 6MWT distance.

Comments: This was not an easy study and data were difficult to come by. By means of study investigations including lung function tests and cardiac catheterization at baseline and at one year follow up, the group had nicely demonstrated a significant worsening of pulmonary arterial pressure in a cohort of subjects with ILD and such significant worsening also correlated with physiological changes as shown in terms of 6MWT performance and pulmonary function test parameters.

YI8 (JRS Young Investigators)

Mechanisms of autophagic regulation of myofibroblast differentiation in IPF pathogenesis

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ABSTRACT:

Background and Aim of Study: Fibroblastic foci (FF), known to be the leading edge of fibrosis development in idiopathic pulmonary fibrosis (IPF), are mainly composed of fibrogenic myofibroblasts. We have recently reported the involvement of insufficient autophagy in myofibroblast differentiation in FF. Autophagy, a process of lysosomal self-degradation, has been implicated in selective removal of damaged mitochondria. Thus, insufficient autophagy may result in accumulation of damaged mitochondria accompanied by increased reactive oxygen species (ROS) production. ROS are involved in various intracellular signaling pathways, including myofibroblast differentiation. Hence, we hypothesized that insufficient autophagy may induce myofibroblast differentiation via regulation of mitochondrial ROS production.

Methods: To explore the regulatory role of autophagy in mitochondrial ROS production and its involvement in myofibroblast differentiation, *in vitro* cell culturing models of human lung fibroblasts were used. Autophagy was induced by treatment with Torin1, (an mTOR inhibitor), while transfection of ATG5 siRNA was performed to inhibit autophagy. CM-H2DCFDA and Mitosox Red were used to evaluate total and mitochondrial ROS production and NAC and MitoTEMPO were employed for inhibition of ROS. LY294002, a PI3K inhibitor, and Akt1/2 kinase inhibitor were used to inhibit the PI3K-Akt pathway.

Results: Inhibition of autophagy increased mitochondrial ROS production and concomitantly induced myofibroblast differentiation in lung fibroblasts, which was clearly inhibited by the treatment with NAC or MitoTEMPO. Autophagy inhibition also activated the PI3K-Akt pathway, and both LY294002 and Akt1/2 kinase inhibitor abrogated myofibroblast differentiation. Furthermore, efficient inhibition of the PI3K-Akt pathway by treatment with MitoTEMPO supports the notion that mitochondrial ROS and subsequent activation of the PI3K-Akt pathway are at least partly responsible for myofibrobalst differentiation in the setting of insufficient autophagy.

Conclusion: These findings suggest that insufficient autophagy-induced mitochondrial ROS production with subsequent PI3K-Akt activation is a potent underlying pathology of myofibroblast differentiation in IPF pathogenesis.

Comments: This was a detail mechanistic study demonstrating very well the significance of autophagy in the pathogenesis of myofibroblastic differentiation, which is considered the fore-front pathogenetic or most active foci for the development of IPF. The subsequent signaling mechanisms were also well shown and response of cell models to Torin1 demonstrated. These results were of great potential in exploration of new therapeutic targets or strategy in relation to autophagy in IPF.

YI9 (TSANZ Young Investigator)

Novel noninvasive techniques for assessing dynamic pulmonary vascular function

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ABSTRACT:

Current techniques for assessing pulmonary arterial hypertension (PAH) are mostly performed under resting conditions. Evaluating the pulmonary circulation under dynamic conditions may provide novel pathophysiological insights and allow early detection of PAH.

Aims: We used (1) Dobutamine Stress Echocardiography (DSE) to generate multipoint pressure -flow (P-Q) plots; and (2) Quantitative Single Photon Emission Computed Tomography (SPECT) to assess changes in regional lung perfusion related to postural shift. We hypothesized that in subjects with PAH compared to controls, inochronotropic stress will produce altered P-Q relationships, and the normal gravity-dependent redistribution of lung perfusion will be lost. Methods: (1) Dobutamine infusion (5 mcg/kg/min increments, peak dose 20) was given to generate multipoint P-Q plots. (2) Regional lung perfusion in supine and upright postures were obtained using SPECT. A perfusion redistribution index (PRI) quantified the perfusion shift along the cranial-caudal axis between postures.

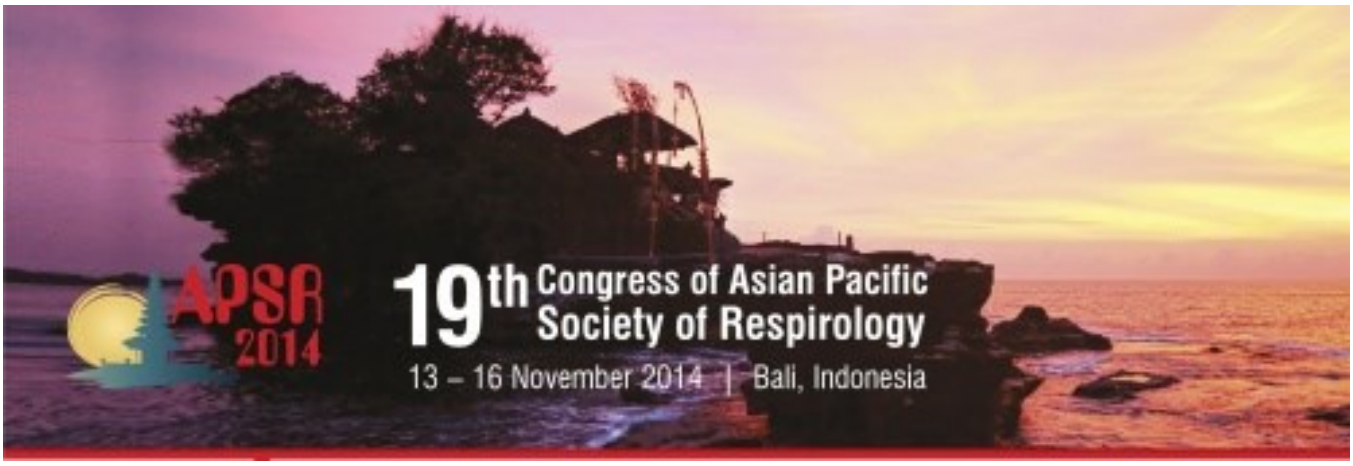
Results: Participants included 16 PAH subjects and 11 healthy controls. Slope of P-Q plots was 5.1±2.7 mmHg/L/min in PAH subjects and 1.1±0.7 mmHg/L/min in controls (p=0.001). P-Q slopes correlated inversely with VO2 peak (r2=0.34, p=0.038). (2) Controls displayed the expected upright cranial-caudal gradient in lung perfusion (left lung 0.29±0.21 cm-1; right lung 0.23±0.22 cm-1) which was abolished on supine posture. PRI was markedly reduced in PAH subjects (0.02±0.06 vs. 0.28±0.15, $p < 0.0001$).

Conclusions: Dynamic techniques reveal pathophysiologic changes in PAH. These can be measured noninvasively and might have a role early disease detection.

Comments: The relatively non-invasive dynamic techniques of using DSE and SPECT scan will offer hope for closer and improved monitoring of clinically significant physiological changes in subjects with PAH. The dynamic techniques also offered additional advantage of assessing any significant changes or aggravation of important physiological parameters reflecting body exercise status and coping with physical stress in subjects with PAH.

Thank you to those who attended the 18th APSR conference!

We hope to see you all next year at the 19th APSR conference in Bali, Indonesia!



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