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## PULMONARY & EXTRA-PULMONARY ARDS: FIZZ OR FUSS?

The acute respiratory distress syndrome (ARDS) was recognized first by Ashbaugh and colleagues(1) in 1967 as a homogenous entity characterized by hypoxemia, low compliance and bilateral pulmonary infiltrates, requiring mechanical ventilation and having a high mortality rate. With progress in understanding and management of this disorder, the American-European consensus conference, in 1994, described two discrete pre-disposing etiological pathways. Pulmonary contusion, inhalational injuries, aspiration, near drowning and fat emboli were described as directly affecting the alveolar epithelium and leading to edema formation whereas sepsis, pancreatitis, massive transfusion and drug overdosage lead to endothelial damage with exudation of fluid into the alveolar space.

This attractive hypothesis remained semantic till Gattinoni elegantly partitioned the low compliance of the respiratory system in ARDS.(2) He showed that the elastance (Est) of the lung [Est (L)] was high in ARDS<sub>p</sub> (Pulmonary, due to a direct cause) and the elastance of the chest wall [Est (W)] was high in ARDS<sub>sexp</sub> (Extra-pulmonary, due to an indirect cause). The raised Est in ARDS<sub>sexp</sub> co-related with the high intra-abdominal pressure seen in these patients. Applications of positive end-expiratory pressure (PEEP) led to recruitment and fall in Est in ARDS<sub>sexp</sub> whereas it led to raised Est in ARDS<sub>p</sub> group. He co-related the prevalence of predominant consolidation in ARDS<sub>p</sub> group and ground glass abnormality (GGO) in ARDS<sub>sexp</sub> group as the pathogenetic mechanism for the observed findings.

This opened a plethora of investigations into the possible difference, if any, between sub-groups of ARDS and their management & prognostic significance. "Splitters" cite distinct etiological events, pathogenetically different mechanisms, different morphology observed, the fact that both are distinguishable physiologically, the varied responses to PEEP and prone pressure ventilation and the different response to inhaled vasodilators.(3-5) "Lumpers" believe

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that etiological case mix is common and practical difficulties in case assignment exist which make dichotomization difficult. Furthermore, current clinical management is similar and the distinction has not been shown to influence the outcome. (6, 7) The current article summarizes the present knowledge in the differences between the two pathogenetic groups of ARDS.

### **Epidemiology of ARDSp and ARDSexp :**

In most studies, ARDSp is more common than ARDSexp. The actual prevalence varies from 47-75% of total. In a study from our centre (N=180), ARDSp (pneumonia most common) accounted for 68.3% (123) and ARDSexp (sepsis most common) for 31.7% (57).(6) In a post-hoc analysis of the NIH ARDS low tidal volume ventilation cohort, (n=902), the incidence of both was equal.(7) The lack of agreement among various studies is because baseline status differs, the prevalence of the disease precipitating ARDS in each center varies, the different impact of therapy and the differing overall and seasonal distribution of these factors in the studied population.(4)

### **Pathogenesis of ARDSp and ARDSexp :**

Pathogenetically, in the early phase, both are distinct. In ARDSp, the injury is localized to the alveolar side, with macrophage and leukocyte activation, with exudation of fluid into the alveolar space. In ARDSexp, the initial damage is to the endothelium, leading to leaky capillaries and interstitial edema. In later stages, the distinction blurs. However, both mechanisms may also be operative, as in pneumonia complicated by sepsis. Direct damage is wrought by pneumonia and indirect damage is by endothelial damage by cytokines.

### **Morphology of ARDSp and ARDSexp :**

The morphological differences between both have been described earlier. The table highlights the same. There are no consistent difference

by which both can be distinguished from each other.(8)

### **Radiology: ARDSp vs. ARDSexp**

The initial observations on frontal radiographs of the differences between the sub-groups of ARDS were by Gattinoni's group. This was followed by computerized tomography (CT) observations in which consolidation and GGO were found to be equally present in ARDSp with asymmetric consolidation being characteristic. Predominant GGO was seen in ARDSexp and was noted to be more symmetric. Pleural effusions were seen in half; Kerley B and pneumatoceles were uncommon.(9) These observations have not been confirmed and a subsequent study failed to show any difference between both.(10)

Pending larger evaluation it can be concluded that increase in the lung densities is most prominent in dependent lung regions in supine position in ARDS. In ARDSp due to CAP two prevalent patterns have been described: Dependent extensive consolidation and air bronchograms with GGO and homogeneous diffuse interstitial and alveolar infiltration, without evidence of atelectasis. In ARDSp due to VAP, densities in the dependent part of the lung (likely atelectasis) are prevalent with the remaining nondependent lung being substantially normal. ARDSexp is characterized by predominant GGO.

### **Respiratory mechanics: ARDSp vs. ARDSexp**

Seminal observations showed that Est (L) was high in ARDSp and the Est (W) was high in ARDSexp. The raised Est in ARDSexp co-related with the high intra-abdominal pressure seen in these patients. The elevated trans-pulmonary pressures and the low pleural pressures in ARDSp pre-disposes these patients to barotrauma. The higher pleural pressures and

lower trans-pulmonary pressures in ARDSexp pre-disposes these patients to hemodynamic compromise.

**Ventilatory strategies: ARDSp vs. ARDSexp**

**1. Efficacy of low tidal volume ventilation**

The efficacy of low tidal volume ventilation and current ventilatory strategies were shown to be independent of the type of ARDS. In a post-hoc analysis of the NIH ARDS low tidal volume ventilation cohort, (n=902), the efficacy of 6 mL/Kg tidal volume ventilation was shown to be uniform.(7)

**2. Application of PEEP and Sigh breaths**

The potential for recruitment is more in atelectasis than in consolidation. Furthermore, applied airway pressure may partition differently, leading to varying recruitment. Use of higher PEEP and higher PI (Cstat<sub>res</sub>) may be safer in ARDSexp since CstatW > CstatL. Also, time course to oxygenation may be different in ARDSp. In clinical practice, though, PEEP is useful in ARDS irrespective of etiology. Clinically, it is possible that both ARDSp and ARDSexp have a mix of consolidation and collapse and preponderance of one does not negate benefit of PEEP. Other mechanisms of benefit, like diversion of ventilation and perfusion, might also have a role.

**3. Prone position ventilation**

Mechanisms by which prone position acts include increase in FRC, changes in diaphragm position/ movement, drainage of secretions, gravity directed blood flow to less injured areas, reduction of heart/ mediastinum compression and changes in chest wall compliance. Given the different physiologies of ARDSp and ARDSexp, varying effect of prone position ventilation can be expected. In a 2-hour physiological study (n=47, 31 ARDSp and 16 ARDSexp), the response in oxygenation was more marked in

ARDSexp compared with ARDSp (3 FOLD), the rate of increase in oxygenation was slower in ARDSp.(11) These observations have been confirmed by another study also.(12)

**Response to pharmacological agents**

The responses to iNo and prostacyclin have been studied in ARDSp and ARDSexp and varied responses have been observed. Though acting by vasodilatation and reduction of intra-pulmonary shunting, the cause of differing data is unclear.(13, 14)

**Long term outcomes different in ARDSp and ARDSexp:**

Mortality is similar in ARDS irrespective of the etiologic pre-disposition. Long term outcomes in ARDSp and ARDSexp are similar, with similar reductions in forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLco).

In summary, prevalent damage in early stages of a direct insult is intra-alveolar whereas in indirect injury is interstitial edema. Radiological pattern in ARDSp is prominent consolidation and ARDSexp is GGO. Primary abnormalities are raised lung and chest wall elastance in ARDSp and ARDSexp respectively. PEEP, inspiratory recruitment and prone position are more effective in ARDSexp. Further studies are warranted to better define if the distinction between ARDS of different origins can improve clinical management and survival.

**Table 1. Morphology of ARDSp and ARDSexp**

Morphology	ARDSp	ARDSexp
Alveoli		
Alveolar epithelium	++Damage	Damage
Altered type I and II cell	++Damage	Normal
Alveolar neutrophils	Prevalent	Rare
Apoptotic neutrophils	Prevalent	Rare
Fibrinous exudates	Present	Rare

Alveolar collapse	++Increased	Increased	risk factors for acute lung injury and the acute respiratory distress syndrome. <i>Am J Respir Crit Care Med.</i> 2001 Jul 15;164(2):231-6.
Local interleukin	Prevalent	Rare	
Interstitial space			
Interstitial oedema	Absent	High	8. Hoelz C, Negri EM, Lichtenfels AJ, Concecao GM, Barbas CS, Saldiva PH, et al. Morphometric differences in pulmonary lesions in primary and secondary ARDS. A preliminary study in autopsies. <i>Pathol Res Pract.</i> 2001;197(8):521-30.
Collagen fibres	++Increased	Increased	
Elastic fibres	Normal	Normal	
Capillary endothelium	Normal	++Damage	
Blood			9. Goodman PC. Radiographic findings in patients with acute respiratory distress syndrome. <i>Clin Chest Med.</i> 2000 Sep;21(3):419-33, vii.
Interleukin	Increased	++Increased	
TNF-	Increased	++Increased	10. Desai SR, Wells AU, Suntharalingam G, Rubens MB, Evans TW, Hansell DM. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary injury: a comparative CT study. <i>Radiology.</i> 2001 Mar;218(3):689-93.

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## NUCLEAR MEDICINE

### TECHNIQUES IN PULMONARY MEDICINE

The single most important application of pulmonary scintigraphy is evaluation of suspected pulmonary embolism. Other indications are quantitative analysis of relative lung perfusion before lobectomy/pneumonectomy and in ARDS.

Ventilation scintigraphy is done with radioactive gases ( $Xe^{133}$ ,  $Xe^{127}$ ) or radioaerosols (DTPA) while perfusion scintigraphy is done with  $Tc^{99m}$  labelled macroaggregates of albumin ( $Tc^{99m}$  MAA) (1)

Common defect seen on ventilation perfusion scan suggestive of pulmonary thromboembolism (PTE) is V/Q mismatch. Based on the site of the defect and no. of defects these defects are classified as high probability, intermediate probability, low probability, very low probability and normal scans. PIOPED study showed that high probability scan had specificity of 97% and sensitivity of 41% for PTE. If the scan was suggestive of low probability, occurrence of PTE was seen in 12% and in normal study it was seen in 4% (2).

A recent meta-analysis has shown that in mod-high pre-test probability situation for PTE high probability V/Q scan, spiral CT positivity and positive compression USG for leg veins have >85% post-test probability for PTE. In low pre-test clinical probability situations if above mentioned results are obtained it requires confirmation by pulmonary angiography (3).

Gallium-67 use has declined over last decade because of lack of specificity, delay between injection and imaging time and relatively poor imaging characteristics.

Gallium-67 has avid uptake in lymphoma, lung cancer, sarcoma and melanoma. In lymphoma it has 86-95% sensitivity and 100%

specificity for staging while it has a sensitivity of 96% and 80% specificity in diagnosis of residual disease. Specificity is lowered by inflammatory changes.

In lung cancer, Ga-67 scan has 86-97% sensitivity for tumor identification and staging. However, specificity is low. Its role in staging and assessment of response to therapy has reduced. It is useful in situations where there is no access to PET studies (4).

Ga-67 uptake is generally associated with cellular inflammation rather than fibrosis. In sarcoidosis, Ga scan has sensitivity of 60-90% for diagnosis but has poor specificity. Combination of Negative Ga Scan and SACE levels excludes diagnosis of sarcoidosis. In IPF, Ga uptake is associated with increased acute cellular proliferation and metabolism, while there is minimal uptake in fibrotic element. Recent major reviews of IPF do not advocate a role of Ga scan in diagnosis of IPF, monitoring disease progression or predicting therapeutic response (5).

In infectious diseases, Ga Scan is not used routinely. However, it can be used occasionally to distinguish active disease from scarring or when no other source of infection is apparent.

PET studies have been useful in characterization of SPN. PET scan has a sensitivity of 83-100% and specificity of 52-100%. It can differentiate between benign and malignant SPN. SUV of 2.5 at 1 hr. is used for this purpose. Delayed scans at 2 hrs may contribute to differentiation also (6) (7). In a meta-analysis PET studies were found to be accurate as a non-invasive imaging test for diagnosis of pulmonary nodules and mass lesions (8).

In staging, PET has been found to be useful in staging of mediastinum and for distant

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metastasis. In mediastinum PET has 84% sensitivity and 93% specificity. Reed C et al, showed that PET studies can prevent non-therapeutic thoracotomies in a significant number of patients (10). It allows for improved patient selection but is likely to miss N2 disease at 5,6,7 lymph node stations (11).

False positive results, although infrequent, are usually due to inflammatory pathology. Because these may result in denying a patient potentially curative surgery, it is recommended that invasive surgical staging be done in case of positive PET scan results. PET studies are able to detect 94% of distant metastasis. PET is superior in detection of distant metastasis as compared to other modalities. It is relatively insensitive for cerebral metastasis.

Kahn et al showed superiority of PET over Tc<sup>99m</sup> depreotide in staging of lung cancer (12). It also helps in effecting a management change (20-40% of cases), is cost effective for staging in NSCLC and is useful in detection of recurrent disease. In non-malignant disorders, PET studies are positive in infective/inflammatory lesions with a sensitivity and specificity of 92% and 100% respectively. It may be useful in identifying correct location for further investigations like biopsy, or aspiration (13).

In pleural disease it can be used to differentiate benign from malignant pleural thickening and for diagnosis and staging of mesothelioma.

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## JOURNAL CLUB CRITIQUE

Calverley PMA, Anderson JA, Celli B, et al for the TORCH (Towards a Revolution in COPD Health) investigators. Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2007; 356: 775-789

### Abstract

**Background :** Long-acting beta-agonists and inhaled corticosteroids are used to treat chronic obstructive pulmonary disease (COPD), but their effect on survival is unknown.

**Methods :** We conducted a randomized, double-blind trial comparing salmeterol at a dose of 50 µg plus fluticasone propionate at a dose of 500 µg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone for a period of 3 years. The primary outcome was death from any cause for the comparison between the combination regimen and placebo; the frequency of exacerbations, health status, and spirometric values were also assessed.

**Results :** Of 6112 patients in the efficacy population, 875 died within 3 years after the start of the study treatment. All-cause mortality rates were 12.6% in the combinationtherapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The hazard ratio for death in the combination-therapy group, as compared with the placebo group, was 0.825 (95% confidence interval [CI], 0.681 to 1.002;  $P = 0.052$ , adjusted for the interim analyses), corresponding to a difference of 2.6 percentage points or a reduction in the risk of death of 17.5%. The mortality rate for salmeterol alone or fluticasone propionate alone did not differ significantly from that for placebo. As compared with placebo, the combination regimen reduced the annual rate of exacerbations from

1.13 to 0.85 and improved health status and spirometric values ( $P < 0.001$  for all comparisons with placebo). There was no difference in the incidence of ocular or bone side effects. The probability of having pneumonia reported as an adverse event was higher among patients receiving medications containing fluticasone propionate (19.6% in the combination-therapy group and 18.3% in the fluticasone group) than in the placebo group (12.3%,  $P < 0.001$  for comparisons between these treatments and placebo).

**Conclusions :** The reduction in death from all causes among patients with COPD in the combination therapy group did not reach the predetermined level of statistical significance. There were significant benefits in all other outcomes among these patients.

### Summary

This was a randomized double-blind clinical trial involving the use of inhaled corticosteroids (ICS) long-acting b-agonists (LABA) or both among patients with moderate to severe COPD (mean FEV1 values being approximately  $44 \pm 12$  % of predicted). Its results suggest that patients receiving a combination of the two drugs used in the current study namely salmeterol (LABA) and fluticasone (ICS) had significantly better improvements in health related quality of life (HRQOL) as well as lung functions (FEV1 values) compared to either of the drugs alone. The combination group also had a lesser frequency of moderate to severe acute exacerbations compared to groups receiving either of the drugs alone. However, there was an increase in the incidence of adverse events (AdvEs) among patients receiving ICS (alone or in combination with LABA). These included local AdvEs like oropharyngeal candidiasis and dysphonia as well as systemic AdvEs like pneumonia.

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## Limitations and Unresolved Issues

An important limitation of the current study was that the primary outcome objective for which the study was designed, namely reduction in mortality, was not achieved with the use of ICS-LABA combination. Moreover, this lack of benefit on survival was also observed in groups wherein these drugs were used singly. Actually this limitation may also be interpreted as its strength – it confirmed that no form of pharmacotherapy has been able to improve survival among COPD patients till date.

A recently published pooled analysis of individual patient data from seven randomized trials (involving 5085 patients) had compared the effects of ICS and placebo in patients with stable COPD (mean baseline FEV<sub>1</sub> values being approximately 59 ± 19 % predicted). In this analysis, ICS reduced all-cause mortality in a mean follow up period of 26 months [adjusted hazard ratio (HR) = 0.73; 95% confidence interval (CI) 0.55 to 0.96]; the benefit being more marked in women and former smokers. However, the authors had commented that further studies were required to determine whether the survival benefits observed in their analysis persisted if the follow up was for a longer time period.

The last word however has not yet been said about ICS and mortality in COPD. A trend towards reduced cardiovascular mortality and lung cancer prevention has been shown in recent studies that require confirmation/validation in future randomized controlled trials.

## Implications for day-to-day practice

1. Patients with moderate and severe COPD may benefit by the use of ICS-LABA combinations that utilize high doses of ICS ( $\geq 500$  ug of fluticasone per day) in the form of reduced frequency of exacerbations as well as improvement in spirometric values and HRQOL.
2. Use of ICS should be avoided in patients with mild COPD in view of the increased incidence of local AdvEs and pneumonia.

## References and Suggested Reading

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