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EDITORIAL

Acute kidney injury classification: AKIN and RIFLE criteria in critical patients

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Abstract

Acute kidney injury (AKI) is a common and serious complication in critically ill patients. The mortality rate remains high despite improved renal replacement techniques. A possible cause of the high mortality rate is that intensive care unit patients tend to be older and more debilitated than before. Pathophysiological factors associated with AKI are also implicated in the failure of other organs, indicating that AKI is often part of a multiple organ failure syndrome. Until recently, there was a lack of consensus as to the best definition, characterization, and evaluation of acute renal failure. This lack of a standard definition has been a major impediment to progress in clinical and basic research. The introduction of the risk, injury, failure, loss, and end-stage kidney disease criteria and the modified version proposed by the Acute Kidney Injury Network have increased the conceptual understanding of AKI syndrome, and these criteria have been successfully tested in clinical studies. This article reviews current findings concerning the application of these criteria for assessing epidemiology and predicting outcome in specific homogeneous critically ill patient groups.

Key words: Acute kidney injury; Extracorporeal membrane oxygenation; Cirrhosis; Sepsis; Acute respiratory distress syndrome; Intensive care unit

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INTRODUCTION

Acute kidney injury (AKI) is well recognized for its impact on intensive care unit (ICU) patient outcomes[1-3]. In an international survey, more than 200 different definitions of AKI were reported[4]. The numerous definitions cause clinical confusion and complicate data comparison[5,6]. The risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure (RIFLE) criteria was published by the Acute Dialysis Quality Initiative group in 2004, in an attempt to standardize AKI research[1]. It classified AKI into three categories (risk, injury, and failure) according to the status of serum creatinine (SCr) and urine output (UO) (Table 1).

In 2007, the Acute Kidney Injury Network (AKIN) group proposed a modified version of the RIFLE criteria. In AKIN stage-1 (analogous to RIFLE-Risk), a smaller change within 48 h in SCr of over 0.3 mg/dL (≥ 26.2 μmol/L) was suggested as the threshold for AKI

(Table 1). Additionally, patients receiving renal replacement therapy were re-classified as AKIN stage-3 (RIFLE-Failure). Finally, the loss and end-stage kidney disease categories were eliminated in the AKIN classification[7].

To date, the use of the consensus definitions of AKI (RIFLE and AKIN) in the literature has increased substantially[8]. Both classifications have been proven to be useful for diagnosing and classifying the severity of AKI in critical patients. This study reviews their use and validation in specific diagnostic groups.

PATIENTS ON EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) is effective in treating severe, reversible myocardial dysfunction (e.g., myocarditis, cardiomyopathy, or postoperative cardiogenic shock) and for providing a bridge to another treatment modality. AKI developing during ECMO is associated with very poor outcome[9,10], possibly due to accumulated extravascular fluid causing interstitial overload, impaired oxygen transport through tissues, and subsequent organ dysfunction, particularly of the heart, lungs, and brain[11,12].

Lin *et al*[9] retrospectively applied the RIFLE criteria to evaluate forty-six critically ill patients treated by ECMO, most of whom had postcardiotomy cardiogenic shock. The RIFLE was determined only during the first day of ECMO support. A progressive and significant increase in mortality was associated with increasing RIFLE categories among all patients.

The authors further retrospectively reviewed the medical records of seventy-eight critical ill patients on ECMO support[10]. The RIFLE criteria classified 78.2% of the patients as having AKI. Multivariate analysis indicated that acute physiology, age, chronic health evaluation (APACHE) IV and RIFLE classification had independent prognostic significance.

Chen *et al*[13] retrospectively evaluated the outcomes of 102 patients treated with ECMO and identified the relationship between prognosis and AKIN scores obtained at pre-ECMO support (AKIN0-h), and at 24 h (AKIN24-h) and 48 h (AKIN48-h) post-ECMO support. The overall mortality rate was 57.8%. The AKIN0-h, AKIN24-h, and AKIN48-h scoring systems also had excellent discrimination power according to analysis of areas under the receiver operating characteristic curves (AUROC). Furthermore, multiple logistic regression analysis indicated that AKIN48-h, age, and Glasgow Coma Scale score on the first day of ICU admission were independent risk factors for hospital mortality. During ECMO support, the AKIN48-h scoring system proved to be a reproducible evaluation tool with excellent prognostic abilities for these patients.

CRITICALLY ILL CIRRHOTIC PATIENTS

A feature of liver cirrhosis is the disturbed systemic circulation characterized by marked arterial vasodilatation occurring principally in the splanchnic circulation. These disturbances may reduce total peripheral vascular resistance and arterial pressure and cause a secondary increase in cardiac output. These abnormalities can cause major cirrhotic complications such as severe liver damage with jaundice, coagulopathy, hepatic encephalopathy, hepatorenal syndrome, hepatocardiac syndrome, and hepatopulmonary syndrome. Renal failure is the most clinically relevant of these conditions as its appearance generally indicates very poor prognosis[14-16].

As demonstrated in a previous prospective study performed by Jenq *et al*[17], the predictors of RIFLE criteria and sequential organ failure assessment (SOFA) score were independently associated with hospital mortality in 134 cirrhotic patients admitted to the ICU. Progressive and significantly elevated mortality correlated with increasing RIFLE criteria severity among all patients. The RIFLE criteria classified 60.4% of ICU cirrhotic patients with varying severity of AKI.

In order to identify specific predictors of hospital mortality in critically ill cirrhotic patients with AKI, Fang *et al*[18] evaluated 111 critically ill cirrhotic patients with AKI (RIFLE-R, I, or F) or a rise in SCr level over 1.5 mg/dL (132.6 μmol/L) using prospectively collected data. Mean arterial pressure (MAP), serum bilirubin, acute respiratory failure, and sepsis on the first day in ICU were significantly related to prognosis. The best Youden index yielded cutoff points of 80 for MAP (in mmHg) and 80 for serum bilirubin (in μmol/L) (or 4.7 mg/dL), and indicated acute respiratory failure and sepsis. A simple model for mortality is developed on the basis of these four readily available parameters on day 1 of ICU admission. The new score (MBRS score: MAP + bilirubin + respiratory failure + sepsis) displays an excellent AUROC (0.898 ± 0.031, $P < 0.001$). The mortality rate exceeds 90% when the MBRS score is 2 or higher.

Moreover, Tu *et al*[19] prospectively evaluated 202 consecutive cirrhotic patients admitted to the ICU during a 2-year period and revealed AKIN, SOFA and the model for end-stage liver disease (MELD) scores showing good discriminative power in predicting hospital mortality in cirrhotic patients admitted to the ICU. The AKIN scoring system proved to be a reproducible evaluation tool with excellent prognostic abilities for these patients.

SEVERE SEPSIS AND SEPTIC SHOCK

The high incidence of sepsis and associated mortality risk in ICU patients are constant concerns[20,21]. Sepsis is also a well-known risk factor for AKI; 35%-50% of AKI cases in ICUs are attributable to sepsis[18,22,23]. Severe sepsis and septic shock are defined according to modified the American College of Chest Physicians and Society of Critical Care Medicine consensus criteria[24]. Patients with proven or suspected infection, two or more systemic inflammatory response syndrome criteria and an infection-induced organ dysfunction are classified as having severe sepsis.

Table 1 Risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure and Acute Kidney Injury Network classification schemes for acute kidney injury

	GFR criteria	Urine output criteria
RIFLE (an acute rise in SCr over 7d)		
Risk	Increase in SCr ⩾ 1.5 × baseline or decrease in GFR ⩾ 25%	UO < 0.5 mL/kg per hour × 6 h
Injury	Increase in SCr ⩾ 2.0 × baseline or decrease in GFR ⩾ 50%	UO < 0.5 mL/kg per hour × 12 h
Failure	Increase in SCr ⩾ 3.0 × baseline or SCr ⩾ 4.0 mg/dL (354 μmol/L) or decrease in GFR ⩾ 75%	UO < 0.3 mL/kg per hour × 24 h or anuria × 12 h
Loss	Complete loss of kidney function > 4 wk	
ESKD	End stage renal disease (> 3 mo)	
AKIN (an acute rise in SCr within 48 h)		
Stage 1	Same as RIFLE-Risk plus increase in SCr ⩾ 0.3 mg/dL (⩾ 26.4 μmol/L)	Same as RIFLE
Stage 2	Same as RIFLE-Injury	
Stage 3	Same as RIFLE-Failure plus initiation of RRT	

AKIN: Acute Kidney Injury Network; ESKD: End-stage kidney disease; GFR: Glomerular filtration rate rate; RIFLE: Risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure; RRT: Renal replacement therapy; SCr: Serum creatitine; UO: Urine output.

Septic shock is diagnosed when the systolic arterial blood pressure remains < 90 mmHg or shows a reduction of > 40 mmHg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension[25].

Chen *et al*[26] studied a total of 121 sepsis patients admitted to the ICU using prospectively collected data. Mortality of these patients was significantly increased as RIFLE score increased. Septic shock, RIFLE criteria, and number of organ system failures on the first day of ICU admission were independent predictors of hospital mortality according to multiple logistic regression analysis. The RIFLE criteria classified 56.2% of ICU septic patients with varying severity of AKI. Excluding patients who died within 6 mo, the percentage of AKI patients who achieved full recovery of renal function was very high (85%). Of the few studies reporting renal recovery in AKI patients, most indicated that patients usually recover adequate renal function[26,27].

Although RIFLE classification was independently predictive of mortality, the leading causes of death associated with AKI were non-renal complications, typically those related to multi-organ dysfunction. During septic shock, global tissue hypoxia caused by imbalance between systemic oxygen delivery and oxygen demand resulted in renal tubular necrosis, multiple organ failure, and increased mortality[28].

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is commonly diagnosed in ICUs and is frequently associated with AKI. The clinical definition of ARDS is the acute onset of bilateral pulmonary infiltrates, a ratio of arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) of ⩽ 200 mmHg, and pulmonary artery occlusion pressure ⩽ 18 mmHg or no evidence of left atrial hypertension[29]. Numerous risk factors, such as pneumonia, sepsis, and aspiration, are associated with ARDS onset. Although recent reports reveal improving mortality rates in ARDS patients[30,31], morbidity and mortality are still high.

Using retrospectively collected data, Lin *et al*[32] earlier reported that a maximum RIFLE (RIFLEmax) score on ICU days 1 and 3 and on the day of open lung biopsy (OLB) improves the accuracy of outcome prediction in ARDS patients undergoing OLB. To compare the predictive value of outcome scoring systems (APACHE IV, earlier APACHE models, SOFA, RIFLE criteria, Acute Lung Injury score) the authors further retrospectively abstracted data from the medical records of 135 critically ill ARDS patients[33]. Overall mortality rate was 65%. Forward conditional logistic regression identified APACHE IV, alveolar-arterial O2 tension difference, age, sepsis, and RIFLEmax score on ICU days 1 and 3 to be independent predictors of hospital mortality. The APACHE IV score and RIFLEmax score were predictors of hospital mortality in ARDS patients, with APACHE IV demonstrating good prognostic accuracy.

The ARDS patient group represented a population with a high risk of AKI. Clearly, significant crosstalk occurs between the lung and other organs. Ischemia/reperfusion injury to the kidney increases pulmonary vascular permeability[34,35]. Furthermore, ventilator-associated lung injury causes AKI in animal models[36]. Regarding the effect of ARDS on the kidney, mechanical ventilation can induce acute tubular necrosis leading to AKI[37]. In addition, the harmful effects of mechanical ventilation are exacerbated by comorbidities. Renal blood flow is further compromised by a reduced cardiac output, resulting from a high intrathoracic pressure. Moreover, the impact of biotrauma is not limited to the lungs and may cause a systemic inflammatory reaction. Sepsis may increase the severity of these effects. This series of events probably reflects a multifactorial process that can eventually cause AKI.

Of note, intra-abdominal pressure (IAP) has recently been included in the consensus statement as the possible

missing link explaining deterioration of renal function in critically ill patients[38,39]. IAP is an independent risk factor for AKI development and may also explain the cardiorenal syndrome[40-43]. Dalfino *et al*[44] put IAP into relation with RIFLE criteria by showing intra-abdominal hypertension to be an independent predictive factor of acute renal failure, defined as failure class of RIFLE criteria[45,46].

COMPARISON OF AKIN AND RIFLE CRITERIA IN GENERAL ICU

The few studies[47,48] that have compared the AKIN and RIFLE criteria have revealed no substantial differences. Chang *et al*[49] retrospectively investigated 291 critically ill patients and compared performance of the RIFLE and AKIN criteria for diagnosing and classifying AKI and for predicting hospital mortality. Overall mortality rate was 60.8%. Increased mortality was progressive and significant based on the severity of AKIN and RIFLE criteria. The AKIN and RIFLE scoring systems displayed good AUROC (0.720 ± 0.030, P = 0.001; 0.738 ± 0.030, P = 0.001, respectively). Compared with RIFLE criteria, this study indicated that the AKIN classification does not improve the sensitivity and accuracy of outcome prediction in critically ill patients.

REVIEW OF CLINICAL LITERATURE ON AKI AS DEFINED BY THE RIFLE AND AKIN CRITERIA

Ricci *et al*[50] published a systematic review of 24 studies. The majority of the studies looked at patients in general or specialized ICU. Most studies were retrospective in design, and used only the creatinine/GFR criterion. In only 12% of the analyzed population were the creatinine and UO criteria used together. The analysis of pooled data showed a stepwise increase in relative risk for death with increasing AKI severity (Risk, 2.40; Injury, 4.15; Failure, 6.37, with respect to non-AKI patients)[50].

Generally speaking, studies that have used the AKIN criteria rather than the RIFLE criteria did not seem to show any improvement in the sensitivity, robustness and predictive ability in the definition and classification of AKI[51]. The RIFLE and AKIN criteria can detect AKI with high sensitivity and high specificity and describe different severity levels that aim to predict the prognosis of affected patients. They are easy to use in a variety of clinical and research settings, but have several limitations. Both utilize an increase in SCr level from a hypothetical baseline value and a decrease in UO, but these surrogate markers of renal impairment manifest relatively late after injury has occurred and do not consider the nature or site of the kidney injury. New biomarkers such as neutrophil gelatinase-associated lipocalin, interleukin-18, kidney injury molecule-1 and cystatin C have shown promise for early diagnosis and prediction of the prognosis of AKI. As more data become available, they could be incorporated into improved definitions or criteria for AKI in the future[51-53].

CONCLUSION

The RIFLE and AKIN criteria have increased the conceptual understanding of AKI syndrome. They have been successfully tested in clinical studies and used to predict the prognosis of critical patients with AKI. Compared with RIFLE criteria, AKIN criteria do not improve the sensitivity and ability to predict outcome in critically ill patients according to present data.

REFERENCES

1 **Bellomo R**, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8**: R204-R212

2 **Bellomo R**, Kellum JA, Ronco C. Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. *Intensive Care Med* 2007; **33**: 409-413

3 **Ostermann M**, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med* 2007; **35**: 1837-1843; quiz 1852

4 **Ricci Z**, Ronco C, D'Amico G, De Felice R, Rossi S, Bolgan I, Bonello M, Zamperetti N, Petras D, Salvatori G, Dan M, Piccinni P. Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. *Nephrol Dial Transplant* 2006; **21**: 690-696

5 **Schrier RW**, Wang W, Poole B, Mitra A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. *J Clin Invest* 2004; **114**: 5-14

6 **Lameire N**, Van Biesen W, Vanholder R. Acute renal failure. *Lancet* 2005; **365**: 417-430

7 **Mehta RL**, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31

8 **Cruz DN**, Ricci Z, Ronco C. Clinical review: RIFLE and AKIN--time for reappraisal. *Crit Care* 2009; **13**: 211

9 **Lin CY**, Chen YC, Tsai FC, Tian YC, Jenq CC, Fang JT, Yang CW. RIFLE classification is predictive of short-term prognosis in critically ill patients with acute renal failure supported by extracorporeal membrane oxygenation. *Nephrol Dial Transplant* 2006; **21**: 2867-2873

10 **Lin CY**, Tsai FC, Tian YC, Jenq CC, Chen YC, Fang JT, Yang CW. Evaluation of outcome scoring systems for patients on extracorporeal membrane oxygenation. *Ann Thorac Surg* 2007; **84**: 1256-1262

11 **Lin CY**, Chen YC, Tsai FC, Tian YC, Jenq CC, Huang CC, Fang JT, Yang CW. Continuous renal replacement therapy combined with extracorporeal membrane oxygenation in advanced cardiac failure patients. *J Nephrol* 2008; **21**: 789-792

12 **Journois D**. Hemofiltration during cardiopulmonary bypass. *Kidney Int Suppl* 1998; **66**: S174-S177

13 **Chen YC**, Tsai FC, Chang CH, Lin CY, Jenq CC, Juan KC, Hsu HH, Chang MY, Tian YC, Hung CC, Fang JT, Yang CW. Prognosis of patients on extracorporeal membrane oxygenation: the impact of acute kidney injury on mortality. *Ann Thorac Surg* 2011; **91**: 137-142

14 **Schrier RW**, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988; **8**: 1151-1157
15 **Martin PY**, Ginès P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. *N Engl J Med* 1998; **339**: 533-541
16 **Chen YC**, Ginès P, Yang J, Summer SN, Falk S, Russell NS, Schrier RW. Increased vascular heme oxygenase-1 expression contributes to arterial vasodilation in experimental cirrhosis in rats. *Hepatology* 2004; **39**: 1075-1087
17 **Jenq CC**, Tsai MH, Tian YC, Lin CY, Yang C, Liu NJ, Lien JM, Chen YC, Fang JT, Chen PC, Yang CW. RIFLE classification can predict short-term prognosis in critically ill cirrhotic patients. *Intensive Care Med* 2007; **33**: 1921-1930
18 **Fang JT**, Tsai MH, Tian YC, Jenq CC, Lin CY, Chen YC, Lien JM, Chen PC, Yang CW. Outcome predictors and new score of critically ill cirrhotic patients with acute renal failure. *Nephrol Dial Transplant* 2008; **23**: 1961-1969
19 **Tu KH**, Jenq CC, Tsai MH, Hsu HH, Chang MY, Tian YC, Hung CC, Fang JT, Yang CW, Chen YC. Outcome scoring systems for short-term prognosis in critically ill cirrhotic patients. *Shock* 2011; **36**: 445-450
20 **Schrier RW**, Wang W. Acute renal failure and sepsis. *N Engl J Med* 2004; **351**: 159-169
21 **Ronco C**, Kellum JA, Bellomo R, House AA. Potential interventions in sepsis-related acute kidney injury. *Clin J Am Soc Nephrol* 2008; **3**: 531-544
22 **Oppert M**, Engel C, Brunkhorst FM, Bogatsch H, Reinhart K, Frei U, Eckardt KU, Loeffler M, John S. Acute renal failure in patients with severe sepsis and septic shock--a significant independent risk factor for mortality: results from the German Prevalence Study. *Nephrol Dial Transplant* 2008; **23**: 904-909
23 **Brivet FG**, Kleinknecht DJ, Loirat P, Landais PJ. Acute renal failure in intensive care units--causes, outcome, and prognostic factors of hospital mortality; a prospective, multicenter study. French Study Group on Acute Renal Failure. *Crit Care Med* 1996; **24**: 192-198
24 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864-874
25 **Levy MM**, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; **31**: 1250-1256
26 **Chen YC**, Jenq CC, Tian YC, Chang MY, Lin CY, Chang CC, Lin HC, Fang JT, Yang CW, Lin SM. Rifle classification for predicting in-hospital mortality in critically ill sepsis patients. *Shock* 2009; **31**: 139-145
27 **Ali T**, Khan I, Simpson W, Prescott G, Townend J, Smith W, Macleod A. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol* 2007; **18**: 1292-1298
28 **Lin SM**, Huang CD, Lin HC, Liu CY, Wang CH, Kuo HP. A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. *Shock* 2006; **26**: 551-557
29 **Bernard GR**, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. *Intensive Care Med* 1994; **20**: 225-232
30 **Stapleton RD**, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES, Steinberg KP. Causes and timing of death in patients with ARDS. *Chest* 2005; **128**: 525-532
31 **Liu KD**, Matthay MA. Advances in critical care for the nephrologist: acute lung injury/ARDS. *Clin J Am Soc Nephrol* 2008; **3**: 578-586
32 **Lin CY**, Kao KC, Tian YC, Jenq CC, Chang MY, Chen YC, Fang JT, Huang CC, Tsai YH, Yang CW. The RIFLE score increases the accuracy of outcome prediction in patients with acute respiratory distress syndrome undergoing open lung biopsy. *Respiration* 2009; **77**: 398-406
33 **Lin CY**, Kao KC, Tian YC, Jenq CC, Chang MY, Chen YC, Fang JT, Huang CC, Tsai YH, Yang CW. Outcome scoring systems for acute respiratory distress syndrome. *Shock* 2010; **34**: 352-357
34 **Liu KD**, Glidden DV, Eisner MD, Parsons PE, Ware LB, Wheeler A, Korpak A, Thompson BT, Chertow GM, Matthay MA. Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. *Crit Care Med* 2007; **35**: 2755-2761
35 **Kramer AA**, Postler G, Salhab KF, Mendez C, Carey LC, Rabb H. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. *Kidney Int* 1999; **55**: 2362-2367
36 **Imai Y**, Parodo J, Kajikawa O, de Perrot M, Fischer S, Edwards V, Cutz E, Liu M, Keshavjee S, Martin TR, Marshall JC, Ranieri VM, Slutsky AS. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA* 2003; **289**: 2104-2112
37 **Kuiper JW**, Groeneveld AB, Slutsky AS, Plötz FB. Mechanical ventilation and acute renal failure. *Crit Care Med* 2005; **33**: 1408-1415
38 **De Waele JJ**, De Laet I, Kirkpatrick AW, Hoste E. Intra-abdominal Hypertension and Abdominal Compartment Syndrome. *Am J Kidney Dis* 2011; **57**: 159-169
39 **Brochard L**, Abroug F, Brenner M, Broccard AF, Danner RL, Ferrer M, Laghi F, Magder S, Papazian L, Pelosi P, Polderman KH. An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med* 2010; **181**: 1128-1155
40 **De laet I**, Malbrain ML, Jadoul JL, Rogiers P, Sugrue M. Renal implications of increased intra-abdominal pressure: are the kidneys the canary for abdominal hypertension? *Acta Clin Belg Suppl* 2007; **1**: 119-130
41 **Sugrue M**, Balogh Z, Malbrain M. Intra-abdominal hypertension and renal failure. *ANZ J Surg* 2004; **74**: 78; discussion 78
42 **Sugrue M**, Buist MD, Hourihan F, Deane S, Bauman A, Hillman K. Prospective study of intra-abdominal hypertension and renal function after laparotomy. *Br J Surg* 1995; **82**: 235-238
43 **Sugrue M**, Jones F, Deane SA, Bishop G, Bauman A, Hillman K. Intra-abdominal hypertension is an independent cause of postoperative renal impairment. *Arch Surg* 1999; **134**: 1082-1085
44 **Dalfino L**, Tullo L, Donadio I, Malcangi V, Brienza N. Intra-abdominal hypertension and acute renal failure in critically ill patients. *Intensive Care Med* 2008; **34**: 707-713
45 **Mullens W**, Abrahams Z, Francis GS, Taylor DO, Starling RC, Tang WH. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. *J Card Fail* 2008; **14**: 508-514
46 **Mullens W**, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, Paganini E, Tang WH. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? *J Am Coll Cardiol* 2008; **51**: 300-306
47 **Lopes JA**, Fernandes P, Jorge S, Gonçalves S, Alvarez A, Costa e Silva Z, França C, Prata MM. Acute kidney injury in intensive care unit patients: a comparison between the

RIFLE and the Acute Kidney Injury Network classifications. *Crit Care* 2008; **12**: R110

48 **Bagshaw SM**, George C, Bellomo R. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008; **23**: 1569-1574

49 **Chang CH**, Lin CY, Tian YC, Jenq CC, Chang MY, Chen YC, Fang JT, Yang CW. Acute kidney injury classification: comparison of AKIN and RIFLE criteria. *Shock* 2010; **33**: 247-252

50 **Ricci Z**, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. *Kidney Int* 2008; **73**: 538-546

51 **Ricci Z**, Cruz DN, Ronco C. Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. *Nat Rev Nephrol* 2011; **7**: 201-208

52 **Coca SG**, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int* 2008; **73**: 1008-1016

53 **Chen TH**, Chang CH, Lin CY, Jenq CC, Chang MY, Tian YC, Hung CC, Fang JT, Yang CW, Wen MS, Lin FC, Chen YC. Acute kidney injury biomarkers for patients in a coronary care unit: a prospective cohort study. *PLoS One* 2012; **7**: e32328

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OBSERVATION

Eisuke Kagawa, MD, *Series Editor*

Extracorporeal cardiopulmonary resuscitation for adult cardiac arrest patients

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Abstract

Cardiac arrest is a major cause of unexpected death in developed countries, and patients with cardiac arrest generally have a poor prognosis. Despite the use of conventional cardiopulmonary resuscitation (CPR), few patients could achieve return of spontaneous circulation (ROSC). Even if ROSC was achieved, some patients showed re-arrest and many survivors were unable to fully resume their former lifestyles because of severe neurological deficits. Safar *et al* reported the effectiveness of emergency cardiopulmonary bypass in an animal model and discussed the possibility of employing cardiopulmonary bypass as a CPR method. Because of progress in medical engineering, the system of veno-arterial extracorporeal membrane oxygenation (ECMO) became small and portable, and it became easy to perform circulatory support in cardiac arrest or shock patients. Extracorporeal cardiopulmonary resuscitation (ECPR) has been reported to be superior to conventional CPR in in-hospital cardiac arrest patients. Veno-arterial ECMO is generally performed in emergency settings and it can be used to perform ECPR in patients with out-of-hospital cardiac arrest. Although there is no sufficient evidence to support the efficacy of ECPR in patients with out-of-hospital cardiac arrest, encouraging results have been obtained in small case series.

Key words: Extracorporeal membrane oxygenation; Extracorporeal cardiopulmonary resuscitation; Conventional cardiopulmonary resuscitation; Return of spontaneous circulation

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INTRODUCTION

Cardiac arrest is a major cause of unexpected death in developed countries, and patients with cardiac arrest generally have a poor prognosis[1,2]. In 1960, artificial ventilation (mouth-to-mouth), chest compression, and electrical defibrillation were integrated into clinical practice. These methods were rediscovered rather than developed from scratch and were used for resuscitation of cardiac arrest patients[3,4]. However, few patients could achieve return of spontaneous circulation (ROSC) with conventional cardiopulmonary resuscitation (CPR). Moreover, despite achieving ROSC, some patients showed re-arrest and many survivors were unable to fully resume their former lifestyles because of severe neurological deficits.

Pretto *et al*[5] and Safar *et al*[6] reported the effectiveness of emergency cardiopulmonary bypass for CPR in an animal model, and discussed the possibility of employing cardiopulmonary bypass as a CPR method. However, the system used for extracorporeal assist circulation was cumbersome and not easily available; therefore, it was only used for experimental methods. Recent progress

in medical engineering has enabled the development of centrifugal pumps, membrane oxygenators, and thin wall cannulae, which provide easy percutaneous cannulation of the femoral artery and vein. Therefore the cardiopulmonary bypass system has now become small and portable and circulatory support can be easily provided to cardiac arrest or shock patients. In 1983, Phillips *et al*[7] performed extracorporeal cardiopulmonary resuscitation (ECPR) using a system comprising thin wall cannulae that enable percutaneous cannulation and a centrifugal pump in 5 patients, of whom 3 patients survived. In 1989, the International Resuscitation Research Center began clinical studies and reported favorable results: 40 of 187 patients (21%) survived[8]. Veno-arterial extracorporeal membrane oxygenation (ECMO), also known as percutaneous cardiopulmonary bypass, emergency cardiopulmonary bypass, portable cardiopulmonary bypass, or percutaneous cardiopulmonary support, provide rapid temporal circulatory assistance to patients with shock or cardiac arrest. Martin *et al*[9] reported that percutaneous cardiopulmonary bypass could be initiated in emergency department. Veno-arterial ECMO is performed in emergency departments and can be used for performing ECPR in patients with out-of-hospital cardiac arrest[9-11]. Recently, Chen *et al*[12,13] reported that ECPR is superior to conventional CPR in in-hospital cardiac arrest patients. Although there is no sufficient evidence to support the efficacy of ECPR in out-of-hospital cardiac arrest patients, encouraging results have been obtained in small case series[10,11,14]. The recently published CPR guidelines recommend ECPR for patients with limited cardiac arrest that may be caused by accidental hypothermia or drug toxicity[15,16]. Further studies are necessary to assess the efficacy and feasibility of ECPR in out-of-hospital cardiac arrest patients.

ECMO SYSTEMS

The ECMO system comprises a centrifugal pump, a membrane oxygenator, a heat exchanger, and bypass cannulae (Figure 1A). A membrane oxygenator oxygenates the blood. To rapidly establish circulatory support, the system should be portable. The centrifugal pump for ECMO is small compared with that used in cardiopulmonary bypass for cardiovascular surgery. The veno-arterial ECMO circuit extends from the cannula (inserted from the femoral vein) in the right atrium to the femoral artery and facilitates artificial blood circulation. Arfitifical oxygenation *via* an oxygenator is necessary, because pulmonary blood circulation is bypassed.

Both roller and centrifugal pumps are used in cardiopulmonary bypass, while only the centrifugal pump is used in veno-arterial ECMO. The roller pump is simple and blood flow is proportional to the number of rounds. The roller pump creates aspiration pressure strong enough to cause haemolysis or air aspiration if the amount of blood aspirated by the venous cannula is insufficient.

The venous blood aspirated by the venous cannula from the right atrium was oxygenated and returned to the femoral artery in veno-arterial ECMO.

Percutaneous cannulation performed by the widely known Seldinger technique facilitates initiation of veno-arterial ECMO. Arterial cannulae measuring 15-17 French and venous cannulae measuring 17-19 French are usually used. The centrifugal pump pressure is lost largely in these cannulae. If the cannulae are not sufficiently large, haemolysis tends to be severe.

INCLUSION CRITERIA FOR ECPR

Because ECPR is expensive and requires substantial manpower, ECPR cannot be performed for all cardiac arrest patients. Furthermore, the inclusion criteria for ECPR differ in each institution. For example, ECPR has low-grade recommendation in the resuscitation guidelines. The inclusion criteria of ECPR in our hospital are as follows: age of 18-74 years, ventricular fibrillation on electrocardiography during CPR, estimated interval of less than 15 min from the patient's collapse to initiation of resuscitation, presumed cardiac origin or pulmonary embolism as the cause of the arrest, and ROSC not achievable within 20 min of conventional CPR by medical personnel. Patients were excluded if they had a terminal illness preceding the arrest and acute aortic dissection with pericardial effusion observed on echocardiography[10].

ECPR PROCEDURES

The ECPR procedure may be different in each institution because of the use of different software and hardware. The following is the ECPR procedure in Hiroshima City Asa Hospital. The cardiologists and medical engineers there have been trained to set up the ECMO systems within 10 min in all cases. In cases of out-of-hospital cardiac arrest, the physician who receives the telephone call from the out-of-hospital emergency medical personnel evaluates the indication for ECPR and its appropriateness for the patient. The cardiology team prepares for advanced cardiac life support, alerts the catheter laboratory, and prepares the ECMO system before patient arrival. If ECPR is considered appropriate for an out-of-hospital cardiac arrest patient who had not achieved ROSC on arrival to the hospital, advanced cardiac life support is continued according to the guidelines. If ROSC could not be achieved after a second dose of epinephrine, the patient is administered continuous chest compressions and transferred to the catheter laboratory. The femoral vein and artery are percutaneously cannulated to achieve extracorporeal circulation, and circulatory support is initiated in the catheter laboratory. A similar system of transfer to the catheter laboratory is used to establish ECMO for in-hospital cardiac arrest patients if advanced cardiac life support fails. After following these protocols, emergency coronary angiography, percutaneous coronary intervention (PCI), emergency pulmonary angiography, IABP, pul-

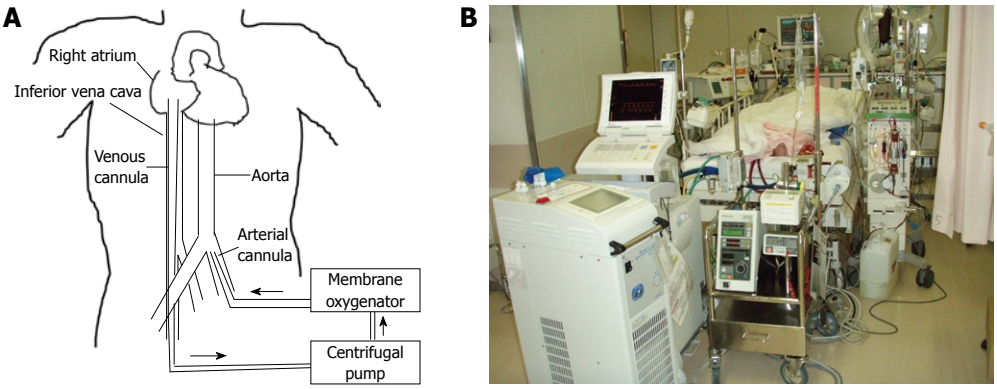

Figure 1 Scheme and picture of the extracorporeal membrane oxygenation system. A: Scheme; B: Picture.

monary angiography and/or placement of a pulmonary artery catheter were performed if necessary, and patients are transferred from the catheter laboratory to the coronary care unit for further intensive care (Figure 1B). Computed tomography is performed during patient transfer from the catheter laboratory to the coronary care unit. In haemodynamically stable comatose patients treated with ECMO, IABP and/or drugs, mild hypothermia is induced by rapid injection of cold saline, surface cooling, using a heat exchanger attached to the ECMO circuit, and/or direct blood cooling by a coil attached to a circuit for continuous haemodiafiltration[10,17,18]. The ECMO circuit is usually primed with cold saline and the heat exchanger can rapidly induced the target temperature of 32-34 ℃ in cardiac arrest patients.

SUBSEQUENT THERAPEUTIC INTERVENTIONS

Chest compression can be ceased after veno-arterial ECMO and pump flow are deemed appropriate. Veno-arterial ECMO allows minimum brain and coronary flow. However, it only provides circulatory support and cannot treat the cause of cardiac arrest: the different causes of cardiac arrest, such as acute coronary syndrome, pulmonary embolism, accidental hypothermia, drug intoxication, and electrolytes disorder, require separate attention. As described above, primary PCI for acute myocardial infarction improves the clinical outcomes. Hence, emergency coronary angiography should be performed in cardiac arrest patients without any obvious external cause of cardiac arrest[19].

Therapeutic hypothermia can improve the clinical outcome in out-of-hospital cardiac arrest patients with ventricular fibrillation, and a similar efficacy is anticipated in in-hospital cardiac arrest patients and cardiac arrest patients whose initial recorded rhythm was non-shockable. Before the initiation of ECMO, rapid injection of cold saline may be feasible and effective[20,21]. The ECMO circuit should therefore be primed with cold saline. After the initiation of ECMO, a heat exchanger can rapidly induce mild hypothermia.

WEANING FROM ECMO

If cardiac function shows improvement, pump flow should be decreased to reduce the left ventricular afterload and risk of haemolysis. If pump flow is decreased to 1.5 L/min and left ventricular ejection time is more than 200 msec, weaning from ECMO should be considered. After additional heparin is administered, the circuit should be clamped for 10 min, and vital signs such as heart rate, blood pressure, pulmonary artery pressure, oxygen saturation, and presence of lethal arrhythmia should be observed. If the above parameters appear abnormal, the circuit should be declamped and circulatory support should be immediately restarted. If the above parameters are within the tolerance levels and there is no lethal arrhythmia, the patient can be weaned from ECMO. The cannulae can be removed surgically or by manual compression. Although surgical removal is safe and reliable, we stop bleeding by manual compression without a low incidence of hematoma because the cannulae became thinner compared to previously used cannulae. If the patient develop refractory shock again after the surgical removal of cannulae, ECMO should be restarted. Re-cannulation may present some difficulty for patients with severe peripheral artery disease.

FUTURE DIRECTIONS

The feasibility and efficacy of ECPR for in-hospital cardiac arrest patients have been reported[13]. However, the feasibility, safety, efficacy, and cost-effectiveness of ECPR for out-of-hospital cardiac arrest patients remain unclear. Further studies are necessary to assess these factors. The rate of favorable recovery remains low in refractory cardiac arrest patients despite being treated with ECPR. Therefore, other novel ideas, methods, or procedures are necessary to enable cardiac arrest patients to resume their former lifestyles.

REFERENCES

1 **Safar P**. Cerebral resuscitation after cardiac arrest: research initiatives and future directions. *Ann Emerg Med* 1993; **22**: 324-349

2 **SOS-KANTO study group**. Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO): an observational study. *Lancet* 2007; **369**: 920-926
3 **Kouwenhoven WB**, Jude JR, Knickerbocker GG. Closed-chest cardiac massage. *JAMA* 1960; **173**: 1064-1067
4 **Safar P**, Escarraga LA, Elam JO. A comparison of the mouth-to-mouth and mouth-to-airway methods of artificial respiration with the chest-pressure arm-lift methods. *N Engl J Med* 1958; **258**: 671-677
5 **Pretto E**, Safar P, Saito R, Stezoski W, Kelsey S. Cardiopulmonary bypass after prolonged cardiac arrest in dogs. *Ann Emerg Med* 1987; **16**: 611-619
6 **Safar P**. Cerebral resuscitation after cardiac arrest: a review. *Circulation* 1986; **74**: IV138-IV153
7 **Phillips SJ**, Ballentine B, Slonine D, Hall J, Vandehaar J, Kongtahworn C, Zeff RH, Skinner JR, Reckmo K, Gray D. Percutaneous initiation of cardiopulmonary bypass. *Ann Thorac Surg* 1983; **36**: 223-225
8 **Hill JG**, Bruhn PS, Cohen SE, Gallagher MW, Manart F, Moore CA, Seifert PE, Askari P, Banchieri C. Emergent applications of cardiopulmonary support: a multiinstitutional experience. *Ann Thorac Surg* 1992; **54**: 699-704
9 **Martin GB**, Rivers EP, Paradis NA, Goetting MG, Morris DC, Nowak RM. Emergency department cardiopulmonary bypass in the treatment of human cardiac arrest. *Chest* 1998; **113**: 743-751
10 **Kagawa E**, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Kurisu S, Nakama Y, Dai K, Takayuki O, Ikenaga H, Morimoto Y, Ejiri K, Oda N. Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support. *Resuscitation* 2010; **81**: 968-973
11 **Nagao K**, Hayashi N, Kanmatsuse K, Arima K, Ohtsuki J, Kikushima K, Watanabe I. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. *J Am Coll Cardiol* 2000; **36**: 776-783
12 **Chen YS**, Chao A, Yu HY, Ko WJ, Wu IH, Chen RJ, Huang SC, Lin FY, Wang SS. Analysis and results of prolonged resuscitation in cardiac arrest patients rescued by extracorporeal membrane oxygenation. *J Am Coll Cardiol* 2003; **41**: 197-203
13 **Chen YS**, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, Chen WJ, Huang SC, Chi NH, Wang CH, Chen LC, Tsai PR, Wang SS, Hwang JJ, Lin FY. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet* 2008; **372**: 554-561
14 **Le Guen M**, Nicolas-Robin A, Carreira S, Raux M, Leprince P, Riou B, Langeron O. Extracorporeal life support following out-of-hospital refractory cardiac arrest. *Crit Care* 2011; **15**: R29
15 **ECC Committee, Subcommittees and Task Forces of the American Heart Association**. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2005; **112**: IV1-203
16 **Deakin CD**, Nolan JP, Soar J, Sunde K, Koster RW, Smith GB, Perkins GD. European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. *Resuscitation* 2010; **81**: 1305-1352
17 **Kagawa E**, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Kurisu S, Nakama Y, Dai K, Otani T, Ikenaga H, Morimoto Y, Ejiri K, Oda N. Who benefits most from mild therapeutic hypothermia in coronary intervention era? A retrospective and propensity-matched study. *Crit Care* 2010; **14**: R155
18 **Kagawa E**, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Kurisu S, Nakama Y, Maruhashi T, Dai K, Matsushita J, Ikenaga H. History of diabetes mellitus as a neurologic predictor in comatose survivors of cardiac arrest of cardiac origin treated with mild hypothermia. *Resuscitation* 2009; **80**: 881-887
19 **Spaulding CM**, Joly LM, Rosenberg A, Monchi M, Weber SN, Dhainaut JF, Carli P. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med* 1997; **336**: 1629-1633
20 **Kim F**, Olsufka M, Longstreth WT, Maynard C, Carlbom D, Deem S, Kudenchuk P, Copass MK, Cobb LA. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. *Circulation* 2007; **115**: 3064-3070
21 **Kim F**, Olsufka M, Carlbom D, Deem S, Longstreth WT, Hanrahan M, Maynard C, Copass MK, Cobb LA. Pilot study of rapid infusion of 2 L of 4 degrees C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. *Circulation* 2005; **112**: 715-719

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REVIEW

Acute respiratory distress syndrome and lung injury: Pathogenetic mechanism and therapeutic implication

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Abstract

To review possible mechanisms and therapeutics for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). ALI/ARDS causes high mortality. The risk factors include head injury, intracranial disorders, sepsis, infections and others. Investigations have indicated the detrimental role of nitric oxide (NO) through the inducible NO synthase (iNOS). The possible therapeutic regimen includes extracorporeal membrane oxygenation, prone position, fluid and hemodynamic management and permissive hypercapnic acidosis *etc*. Other pharmacological treatments are anti-inflammatory and/or antimicrobial agents, inhalation of NO, glucocorticoids, surfactant therapy and agents facilitating lung water resolution and ion transports. β-adrenergic agonists are able to accelerate lung fluid and ion removal and to stimulate surfactant secretion. In conscious rats, regular exercise training alleviates the endotoxin-induced ALI. Propofol and N-acetylcysteine exert protective effect on the ALI induced by endotoxin. Insulin possesses anti-inflammatory effect. Pentobarbital is capable of reducing the endotoxin-induced ALI. In addition, nicotinamide or niacinamide abrogates the ALI caused by ischemia/reperfusion or endotoxemia. This review includes historical retrospective of ALI/ARDS, the neurogenic pulmonary edema due to head injury, the detrimental role of NO, the risk factors, and the possible pathogenetic mechanisms as well as therapeutic regimen for ALI/ARDS.

Key words: Acute lung injury; Acute respiratory distress syndrome; Pathogenetic mechanisms; Therapeutic regimen; Nitric oxide; Inducible nitric oxide synthase

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INTRODUCTION

Acute respiratory distress syndrome (ARDS), the most devastating form of acute lung injury (ALI), is a serious clinical disorder with high mortality (30%-60%)[1-3]. The risk factors for ARDS include septicemia, acid aspiration, infection, traumatic injury, fat embolism, ischemia/reperfusion[3-8], and other causes[9-13]. Our cardiopulmonary laboratory has carried out experimental studies and clinical investigations on ALI and ARDS since 1973[3,12,14-18].

The purposes of this review article are: (1) to describe in brief the historical retrospective of ARDS and ALI; (2) to draw attention to an important clinical issue of neurogenic ALI; (3) to present the experimental studies and clinical investigations from our laboratory from 1973 to 2008; (4) to elucidate the functional role of nitric oxide (NO) and other mediators involved in the pathogenesis of ARDS/ALI; (5) To define the risk factors for ARDS and ALI; and (6) to discuss the pathogenetic mechanisms and therapeutic regimen for ARDS/ALI.

HISTORICAL RETROSPECTIVE OF PULMONARY EDEMA, ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

In 1967, Ashbaugh and colleagues first described 12 adults with respiratory distress syndrome including cyanosis, reduced lung compliance, and diffuse infiltrates evident on chest radiograph[19]. The initial term of this disorder was "adult respiratory distress syndrome"[20]. This entity is now termed "ARDS", since it does occur in children[21,22]. Early reports used "pulmonary edema (PE)" because the edematous lesions in the lungs[23-27]. ARDS is now recognized as an important clinical problem[1,3,28-30].

NEUROGENIC PULMONARY EDEMA-A DRAMATIC PE OR ALI FOLLOWING HEAD INJURY

Cushing[31,32] investigated the changes in arterial pressure (AP), heart rate (HR) and respiration in response to an increased intracranial pressure in anesthetized dogs. The Cushing[31,32] responses including systemic hypertension, bradycardia and irregular respiration (dyspnea and apnea) have been used as signs of intracranial hypertension (ICH). Later studies have elucidated and described the hemodynamic consequences and cardiovascular complications of ICH[14,33,34]. In anesthetized dogs, we employed total heart bypass and found that ICH resulted in constriction of the systemic and pulmonary resistance and capacitance vessels[35]. Spectral analysis of the aortic pressure and flow revealed that ICH caused hemodynamic changes of the steady and pulsatile components. ICH not only increased the AP and total peripheral resistance, but also elevated the arterial impedance, pulse wave reflection and ventricular work with a reduction in arterial compliance[36,37]. Evaluation of the HR variability indicated that ICH was associated with augmented sympathetic and attenuated parasympathetic drive[38]. The most serious cardiopulmonary sequelae is fatal PE associated with hypertensive crisis[39,40]. Weissman *et al*[23] in 1939 presented a comprehensive survey in patients with intracranial hemorrhage. He reported that various degrees of lung edema and congestion were found in 70% of 686 cases with intracranial hemorrhage. Mild lung congestion was found in only 2% of 200 control cases without intracranial lesions. In this report, he also mentioned that Moutier in 1918 was indeed the first to notice severe lung edema in a patient after gunshot injury to the head. In addition, he noted that Hess in 1934 reported several cases of PE in patients with brain tumor, epilepsy and lesions in medulla. Richards *et al*[25] in 1963 reported fatal PE in 46 cases of 88 patients with brain injury. The most severe cases were found in patients with brain stem distortion, hemorrhage and infarction. Subsequent clinical observations[26,41] confirmed the occurrence of severe PE in patients with intracranial disorders. Jourdan *et al*[42] revealed that acute PE could dramatically complicate brain injury in four child cases. Today, this serious clinical problem has been overlooked by most clinicians because: (1) Attention on the brain problem always supercedes the lung condition; and (2) The dramatic, fulminating and fatal outcomes often result in sudden death before any emergent intervention[41].

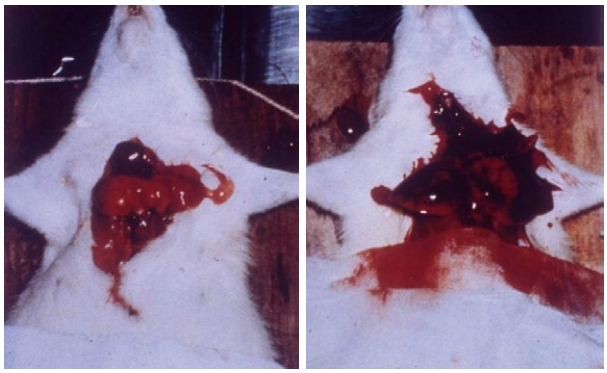

Figure 1 The gross inspection of the lung following cerebral compression in anesthetized rats. The normal lung in a rat without cerebral compression appears pink color and small size (left); Severe pulmonary edema and hemorrhage occur after cerebral compression. The lung is swollen and dark red in color (right).

Experimental evidence of pulmonary hypertension followed by edema formation due to ICH was demonstrated in guinea pigs and dogs[24,43]. Similar observations were described in other animal species including rabbits, monkeys and chimpanzees[27,44,45]. These studies mainly confirmed that PE could be induced in animals following ICH. Little information was provided with respect to the pathogenetic mechanisms of the neurogenic PE. In 1973, we began our extensive studies on the neural and hemodynamic mechanisms of neurogenic PE in anesthetized rats. A rapid mass impact into the cranium or distension of a balloon installed intracranially caused systemic hypertension. Subsequently, the insult produced severe pulmonary changes in 3-5 min after cerebral compression (CC). The lungs showed dark-red discoloration, and were swollen and globular in appearance. This was evidence of gross hemorrhage. The lung weight (LW) was increased 3 to 4-fold the normal value (Figure 1). On microscopic examination, the normal configuration of alveolar structure was obscured. There were air spaces filled with red blood cells and exudate. The perivascular

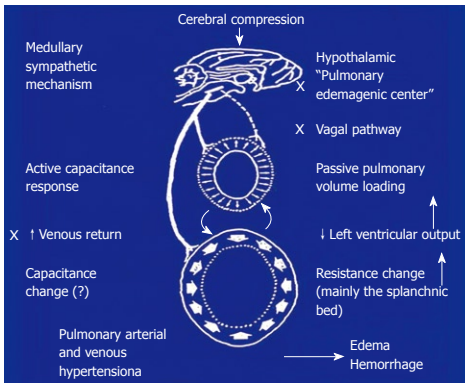

Figure 2 Schematical representation of the neural and hemodynamic mechanisms involved in the pulmonary edema and hemorrhage following cerebral compression. The hypothalamic "pulmonary edemagenic center" and vagal pathway are not important. Activation of the medullary sympathetic mechanism causes vasoconstriction of the systemic resistance and capacitance vessels, resulting in blood shift from the systemic to pulmonary circulation. A dramatic decrease in the left ventricular output produces pulmonary volume loading. Subsequently, pulmonary arterial and venous hypertension ensue, and finally, severe lung edema and hemorrhage.

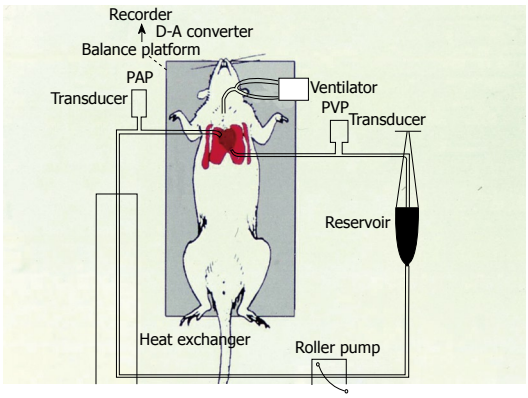

Figure 3 The isolated perfused lung *in situ* preparation. A roller pump provides constant flow. The pulmonary arterial pressure (PAP) and venous pressure (PVP) are monitored by pressure transducers. The change in body weight is determined by a balance platform. The increase in body weight reflects the lung weight gain.

space was distended. Electron-microscopic examination revealed marked stretching of the capillary endothelial cells. Disruption of the entire capillary wall with leakage of red cells from the vessel lumen to the interstitium was observed. In comparison with the other animal studies, our findings presented the most drastic lung changes in terms of rapid onset and severity[14,15]. With respect to the central nervous system that is responsible for the pulmonary sequelae following CC, activation of a "hypothalamic PE genetic center" has been implicated to be involved in the centrogenic PE[46]. In our early studies[14,15], we found that a midcollicular decerebration did not affect the centrogenic PE, suggesting that neural structures above the medulla oblongata were not involved in the genesis of CC-induced PE. Later studies demonstrated that sympathetic overactivation leading to systemic vasoconstriction was the major culprit for PE of centrogenic origin. Complicated hemodynamic measurements and heart bypass design were employed to elucidate the hemodynamic events. Relevant studies revealed that ICH caused vasoconstriction of resistance and capacitance vessels in the systemic and pulmonary circulation. Shift of blood from the systemic vascular beds to the lung was the major cause of pressure and volume loading in the pulmonary circulation[35,47] (Figure 2). The hemodynamic alterations have elaborated the classic Cushing[31,32] responses including systemic hypertension, bradycardia and intermittent apnea.

In support of the blood volume shift from the systemic to pulmonary circulation, we used a scintiphotographic method to demonstrate increased lung blood volume[48]. The scintiphotographic study was performed by intravenous injection of a specific isotope, indium-113m. The radioactive isotope forms a large molecular complex with plasma transferrin and is evenly distributed inside the circulatory system. The lungs normally showed little radioactivity. After CC, an increased radioactivity in the lung was evident, indicating blood accumulation in the pulmonary circulation. Regional sympathectomy demonstrated that the splanchnic beds were the major site of vasoconstriction. Direct sympathetic vasoconstriction in the pulmonary circulation only contributed in part to the centrogenic PE[49,50].

EXPERIMENTAL STUDIES AND CLINICAL INVESTIGATIONS ON ALI/ARDS IN OUR LABORATORY

In the early 1990s, our laboratory collaborated with clinicians in the Chest Medicine, Tri-Service General Hospital, Taipei, Taiwan. Many basic and clinical investigators were trained in the laboratory to study on the mechanisms of PE, ALI and ARDS caused by various challenges and disorders, such as phorbol myristate acetate (PMA), platelets, air embolism, ischemia/reperfusion and other challenges. We developed an isolated rat's lung model that was perfused with constant flow and left *in situ* (Figure 3). The lungs were not needed to remove from the body. In the preparation, the LW to body weight ratio, LW gain, microvascular permeability, protein concentration in bronchoalveolar lavage, tracer dye leakage, pulmonary arterial and venous pressure and pulmonary vascular resistance could be measured or calculated. Furthermore, biochemical factors and inflammatory cytokines were determined. We have used this preparation in many studies for more than 20 years[3,9,17,51-72].

In these studies, isolated lung preparation was used alone or in combination with the whole rodent model. The main findings were that cyclooxygenase products of arachidonic acid such as thromboxane A_2 was involved in the ALI and pulmonary hypertension caused by PMA, air embolism and platelets[51,52]. Furthermore, we found that L-arginine and inhaled NO enhanced the lung injury caused by air embolism, while blockade of NO synthase

(NOS) with N$^{\omega}$-nitro-L-arginine methyl ester (L-NAME) attenuated the ALI[52]. The results suggest that NO is detrimental to the lung in air embolism.

Hypoxia-induced pulmonary vasoconstriction has been a well-known physiological phenomenon. The physiological significance is that capillary blood flow to hypoxic alveoli can be reduced, and the blood flow is thus diverted to oxygenated alveoli. It has been speculated that inadequate NO formation is responsible for the increased vascular tone, pulmonary vasoconstriction and hypertension[17,73]. This contention was challenged by a study in our *in situ* lung preparation[54]. A detector probe for NO was placed in the pulmonary vein and lung tissue in isolated perfused rat's lungs. Real-time NO monitoring revealed that NO release was increased accompanied by pulmonary arterial hypertension following ventilatory hypoxia. Pretreatment with L-arginine potentiated the NO release and reduced the pulmonary hypertension, while L-NAME produced the opposite effects. These findings suggest that continuous NO release from the lung maintains pulmonary arterial pressure (PAP) and that insufficient NO formation is not the cause of hypoxia-induced pulmonary hypertension. In this connection, studies from our laboratory[74,75] also contest the early consensus that impairment of endothelial function and NO formation is the cause of hypertension due to reduction of the vasodilatory effect of NO[17,73].

Recent experimental studies have investigated the role of NO, free radicals and proinflammatory cytokines in the endotoxin-induced pathophysiological and biochemical changes and the associated ALI. Septicemia or endotoxin shock is one of the major causes of death in the United States and other countries[76-78]. Activation of inducible NO synthase (iNOS) to produce a large amount of NO accounts for the systemic hypotension, hyperreactiveness to vasoconstrictors and finally multiple organ failure in endotoxin shock[77-79]. We found that administration of endotoxin [lipopolysaccharide (LPS)] induced ALI with increases in NO, iNOS, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). The findings suggest that NO/iNOS and proinflammatory cytokines are involved in the sepsis-induced ALI[56].

Our research team used the isolated perfused lung model to reveal that the lung was the major source of NO production following endotoxemia[58]. NO production mediated by the iNOS system, is toxic to the endothelium in the pulmonary microvasculature in isolated perfused lungs subjected to ischemia/reperfusion[61]. Administration of red blood cells and hemoglobin into the isolated lung as well as static inflation attenuated the ALI following hypoxia or ischemia/reperfusion[9,57].

We have recently advanced our studies on clinical arena[8,10,80]. In patients with Japanese B encephalitis, viral destruction of the depressor area in the medulla oblongata causes central sympathetic activation, whereas rupture of intracranial mycotic aneurysms results in increased intracranial pressure. The hemodynamic mechanism of ALI or ARDS in these two disorders may operate through the similar sequences as proposed by our previous reports, which related to the ALI caused by ICH[14,47]. We also revealed ARDS in cases of lymphangitis in breast carcinoma and fat embolism. Blockade of lymphatics, capillaries, and venules in breast cancer with lymphangitis caused ALI. In cases of ALI associated with fat embolism, we found that ALI could not be solely attributed to fatty embolic blockade of venous and lymphatic drainage. Several mediators, such as cyclic guanosine monophosphate, 5-hydroxytryptamine (serotonin), NO and cytokines might play a contributing role. Kao and coworkers studied 8 patients who died of fat embolism syndrome (FES) with ARDS[10]. Together with the previous report of 6 cases[80], we had the largest group (a total of 14 patients) of autopsy cases with FES and ARDS. These cases were admitted because of long bone fracture (fracture of tibia, femur, combined fracture and fracture of multiple pelvic bones). The chest radiograph revealed clear lung on admission. Subjects developed signs of respiratory distress and progressive loss of consciousness. Chest X-ray showed lung infiltration. Gross inspection revealed diffuse petechial rashes over the skin. Systemic hypotension and bradycardia ensued. Tachypnea, cyanosis, and cardiac arrest developed. Arterial blood pH and PaO_2 were decreased, whereas an increase in $PaCO_2$ was observed. Despite intensive care and treatment, the patients expired within 3 h after the crush injury. Before death, measurement of PAP disclosed a high PAP. Biochemical determination further indicates that NO, methyl guanidine (an indicator of hydroxyl radicals), phospholipase A_2 are involved in the ARDS due to FES.

During the summers from 2001-2003, we encountered a total of 48 children suffering from hand, foot, and mouth disease[8]. Chest radiography on admission revealed clear lung. However, 21 of these children developed severe dyspnea, hyperglycemia, leukocytosis, and decreased blood oxygen tension. AP and HR fluctuation ensued. Spectral analysis of the AP and HR variabilities showed elevations in sympathetic activity at the onset of respiratory stress. Thereafter, parasympathetic drive increased with declines in AP and HR. These children died within 4 h after the onset of ARDS. Before death, chest radiography revealed severe lung infiltration. Similar to Japanese B encephalitis, destruction of the medullary depressor area caused initial sympathetic activation. Reverse-transcriptase polymerase chain reaction (RT-PCR) found marked iNOS mRNA expression in the lung parenchyma, suggesting iNOS may also be involved in the pathogenesis of ARDS in patients with enterovirus 71 infection.

Furthermore, we have reported ARDS in patients with leptospirosis[13]. In leptospirosis-induced ARDS, histochemical stain demonstrated spirochaetes bacteria in the alveolar space. The pathology included alveolar hemorrhage, myocarditis, portal inflammation and interstitial nephritis. Antigen retrieval immunohistochemical stain disclosed iNOS expression in the alveolar type 1 cells, myocardium, hepatocytes and renal tubules. Spectral

analysis of AP and HR variabilities indicated decreased sympathetic drive with increased parasympathetic activity. The changes in autonomic functions led to severe hypotension and bradycardia. Biochemical determinations suggested multiple organ damage. The pathogenesis of lung and organ injury might also involve iNOS and NO production[13,81]. In subjects with scrub typhus, Orientia tsutsugamushi infection caused alveolar injury. Marked iNOS expression was found in the alveolar macrophages with increase in plasma nitrate/nitrite, suggesting that NO production from the alveolar macrophages accounts for the ALI[82]. The victim from rabies was a woman bitten by a wild dog. In addition to sign of hydrophobia, hypoxia, hypercapnia, hyperglycemia and increased plasma nitrate/nitrite were observed. The woman died of alveolar hemorrhage shortly after admission[83]. Recently, we encountered five cases with long-term malignancy. These subjects displayed signs of respiratory distress following an episode of hypercalcemia. Two cases died of ARDS after the plasma calcium was increased above 6 mmol/L (unpublished data). Holmes *et al*[84], reported a case who died of ARDS following a hypercalcemia crisis caused by a parathyroid adenoma. We conducted animal experiments in whole rodent and isolated perfused rat's lungs. Our results indicated that hypercalcemia (calcium concentration > 5 mmol/L) caused severe ALI in conscious rats and isolated lungs. Immunohistochemical staining showed iNOS activity in the alveolar macrophages and epithelial cells. RT-PCR found marked increase in iNOS mRNA expression in lung parenchyma. Hypercalcemia also increased plasma nitrate/nitrite, methyl guanidine, proinflammatory cytokines and procalcitonin. Pretreatment with calcitonin or L-N^6 (1-iminoethyl)-lysine (L-Nil, an iNOS inhibitor) attenuated the hypercalcemia-induced changes. We proposed that hypercalcemia produced a sepsis-like syndrome. The ALI caused by hypercalcemia may involve NO and iNOS[85].

THE DETRIMENTAL ROLE iNOS-GENERATED NO IN ALI/ARDS

The aforementioned animal studies and clinical observations indicated that NO production through the iNOS may be involved in the lung injury due to various causes. Our research team demonstrated that endotoxemia produced in anesthetized rats by intravenous administration of LPS (endotoxin) provoked systemic hypotension, endothelial damage and ALI accompanied by increased plasma nitrate/nitrite and expression of iNOS mRNA, TNF-α and IL-1β. The LPS-induced changes were abolished by nonspecific and iNOS-specific (iNOS) inhibitors such as N^{ω}-monomethyl-L-arginine, L-NAME, aminoguanine and dexamethasone[56]. This study suggested that NO/iNOS, TNF-α and IL-1β were involved in the endotoxemia-induced ALI. Generation of NO by the activated neutrophil caused alveolar injury from smoke inhalation[86]. Many laboratories using specific iNOS inhibitors and/or iNOS-knockout animals have supported the contention that NO/iNOS is responsible for the oxidative stress and endothelial damage in the ARDS/ALI caused by endotoxin, ozone exposure, carrageenan treatment, acute hypoxia, bleomycin administration, acid aspiration and other challenges[11,87-96]. Our laboratory further provided evidence to suggest that the NO/iNOS system is involved in the pathogenesis of ALI caused by air embolism[71], fat embolism[10,97,98], ischemia/reperfusion[67], oleic acid[99], and PMA[100]. In these recent studies, various insults caused increase in nitrate/nitrite in plasma or lung perfusate, upregulation of iNOS mRNA in lung parenchyma accompanied with elevation of proinflammatory cytokines such as TNF-α, IL-1β and IL-6. Lin *et al*[101] have suggested that an increase in iNOS mRNA triggers the release of proinflammatory cytokines in septic and conscious rats. The inflammatory responses results in multiple organ damage including ALI. Inhibition of iNOS with *S*-methylisothiourea or L-N^6-(iminoethyl)-lysine (L-Nil) attenuated the inflammatory changes, release of NO and cytokines, thereby preventing the organ dysfunction and ALI[65].

RISK FACTORS AND PATHOGENETIC MECHANISMS

In animal experimentations and clinical investigations, the risk factors causing ALI/ARDS include head injury, ICH[14,15,23,25-27,39,42,47], sepsis[7,13,56,58,63,64,68,87,89,92,94,102], and infections[4-8,13,30,80-83]. Pulmonary embolic disorders such as fat and air embolism are less common causes[1,10,52,71,80,103,104]. Ischemia/reperfusion lung injury may develop as a consequence of several pulmonary disorders such as pulmonary artery thromboendarterectomy, thrombolysis after pulmonary embolism and lung transplantation[9,61,67,105-107]. Gastric aspiration occurs frequently in surgical patients under anesthesia and other causes such as blunt thoracic trauma, impaired glottis competency, and pregnancy[108-110]. It is one of the major causes of ARDS[111,112]. Intratracheal instillation of hydrochloric acid or gastric particles has been employed as experimental model of ALI[11,113-115]. In addition, amphetamine and oleic acid have been employed for the induction of ALI[59,99,116,117]. PMA (12-O-tetradecanoyl-phorbol-13-acetate), an ester derivative from croton oil has been used to induce ALI[60,69,118,119]. Experiments *in vivo* and *in vitro* have demonstrated that PMA is a strong neutrophil activator[119-122]. Activation and recruitment of neutrophils that lead to release of neutrophil elastase and other mediators may play an initial role in the pathogenesis of ALI[123,124].

The oleic acid-induced ALI has several clinical implications. First, the blood level of oleic acid was significantly elevated in patients with ARDS[125,126]. Second, the proportion of oleic acid incorporated into surfactant phospholipids was also increased in patients with ARDS and sepsis[127,128]. These observations suggest that serum level of oleic acid may be a predictor or prognostic factor for ARDS[116,125]. Early study focused on the potential toxic effects of high oxygen fractions on inspired air[129].

Ventilator-induced ALI was attributed to the deleterious effects on capillary stress due to alveolar overdistension. Cyclic opening and closing of atelectatic alveoli during mechanical ventilation might exacerbate lung injury by damaging alveoli. Recent evidence indicated that overdistension coupled with repeated collapse and reopening of alveoli initiated an inflammatory cascade of proinflammatory cytokines release[1,29,130,131].

In spite of the risk factors and causes, the pathophysiology of ARDS/ALI is generally considered to be initiated by formation of alveolar edema (even hemorrhage) that is enriched with protein, inflammatory cells or red blood cells. After damage of alveolar-capillary barrier, impairment of gas exchange occurs, with decrease in lung compliance and increases in dispersion of ventilation and perfusion and intrapulmonary shunt. Hypoxia, reduction in arterial oxygen pressure to fraction of oxygen in inspired air (PaO_2/FiO_2), and hypercapnia ensued despite ventilation with high oxygen[1,3,28,30,132]. In addition to the potential toxic effects of NO and free radicals, certain chemokines, cytokines, neutrophil elastase, myeloperoxidase and malondialdehyde have been shown to be associated with several types of ARDS/ALI[99,124,133-135]. The balance between proinflammatory and anti-inflammatory mediators is regulated by transcriptional factors mainly nuclear factor-κB[136]. Pulmonary fluid clearance and ion transport are important factors to determine the extent of lung edema. Regulator factors include cystic fibrosis transmembrane conductance regulators, sodium- and potassium-activated adenosine triphophatase, protein kinases, aclenylate cyclase, and cyclic adenosine monophosphate[7,81,137,138].

POSSIBLE THERAPEUTIC REGIMEN

The treatment of ARDS/ALI is difficult and complex. Several review articles and monographs have addressed the issue of possible therapeutic regimen. The modalities include extracorporeal membrane oxygenation, prone position, mechanical ventilation with appropriate tidal volume and respiratory pressure, fluid and hemodynamic management and permissive hypercapnic acidosis[1,29,139-150].

Other pharmacological treatments are anti-inflammatory and/or antimicrobial agents to control infection and to abrogate sepsis, adequate nutrition, surfactant therapy, inhalation of NO and vasodilators, glucocorticoids and nonsteroid anti-inflammatory drugs, and agents that accelerate lung water resolution and ion transports[1,151-154]. Although most animal studies on these pharmacological options showed favorable results, the effectiveness and outcomes in clinical studies or trials were conflicting[1,12,22].

β-adrenergic agnoists to facilitate water removal and ion transport have been shown to be promising. These agents may also stimulate secretion of surfactant and have no serious side effects. There were several reports on the pharmacological and molecular actions of β agonists, surfactant, vascular endothelial growth factor and related molecules as well as angiotensin-converting enzyme[155,156].

NONPHARMACOLOGICAL AND PHARMACOLOGICAL TREATMENTS FOR ALI AND ARDS FROM RECENT STUDIES IN OUR LABORATORY

In addition to the experimental studies and clinical investigations on the pathogenesis of ALI/ARDS, our laboratory has carried out several experimentations on the therapeutic regimen for this serious disorder. In conscious rats, regular exercise training attenuates septic responses such as systemic hypotension, increases in plasma nitrate/nitrite, methyl guanidine, blood urea nitrogen, creatinine, amylase, lipase, asparate aminotransferase, alanine aminotransferase, creatine phosphokinase, lactic dehydrogenase, TNF-α, and IL-1β. Exercise training also abrogates the cardiac, hepatic and pulmonary injuries caused by endotoxemia[64]. Insulin exerts anti-inflammatory effects on the ALI and associated biochemical changes following intravenous administration of LPS[62]. Propofol (2, 6-diisopropylphenol) has been commonly used for sedation in critically ill patients[157]. This anesthetic has rapid onset, short duration and rapid elimination[158]. Propofol protects the anesthetized rats from ALI caused by endotoxin[68]. In conscious rats, oleic acid results in sepsis-like responses including ALI, inflammatory reactions and increased in neutrophil-derived factors (neutrophil elastase, myeloperoxidase and malondialdehyde), nitrate/nitrite, methyl guanidine, and inflammatory cytokines. It depresses the sodium-and potassium-activated ATPase, but upregulates the iNOS mRNA expression. Pretreatment and posttreatment with propofol alleviates or reverses the oleic acid-induced lung pathology and associated biochemical changes[99]. Pentobarbital, an anesthetic agent commonly used in experimental studies and a hyponotics for patients. This agent improves the pulmonary and other organ functions following LPS administration. It also increases the survival rate[66]. A later study by Yang *et al*[159] further revealed that pentobarbital suppressed the expression of TNF-α, which might result from decrease in the activities of nuclear factor-κB and activator protein 1 and reduction in expression of P38 mitogen-activated protein kinase. *In vivo* examination of cytotoxic effects of LPS disclosed that LPS caused multiple organ dysfunctions. These changes were attenuated by pentobarbital. Pentobarbital also reduced the cell aptosis caused by deforoxamine-induced hypoxia. Nicotinamide or niacinamide (compound of soluble B complex) abrogates the ALI caused by ischemic/reperfusion or endotoxin by mechanism through inhibition on poly (ADP-ribose) synthase and subsequent suppression of iNOS. NO, free radicals and proinflammatory cytokines with restoration of adenosine triphosphate[67,72]. N-acetylcysteine, an antioxidant and cytoprotective agent with scavenging action on reactive oxygen species and inhibitory effects on proinflammatory

cytokines ameliorated organ dysfunctions due to sepsis in conscious rats[160,161]. In a similar endotoxin-induced ALI model, we found that N-acetylcysteine improved the LPS-induced systemic hypotension and leukocytopenia. It also reduced the extent of ALI, as evidenced by reductions in LW changes, exhaled NO and lung pathology. In addition, N-acetylcysteine diminished the LPS-induced increases in nitrate/nitrite, TNF-α, and IL-1β[63]. In isolated lungs, N-acetylcysteine attenuated the ALI caused by PMA[69]. In a most recent study, we reported that posttreatment with N-acetylcysteine prevented the ALI caused by fat embolism[98]. Collectively, the results of our studies favored N-acetylcysteine as a therapeutic agent for ALI/ARDS. The conflicting results and practice guidelines from clinical studies in the recommendation of N-acetylcysteine in critically ill patients[162,163] were commented and analyzed by Molnár[164]. The clinical adaptation of results from animal studies requires further investigations.

CONCLUSION

ARDS or ALI is a serious clinical problem with high mortality. The risk factors leading to ALI/ARDS include head injury, intracranial disorders, sepsis and infections. Pulmonary embolic disorders such as fat and air embolism are less common causes. Ischemia/reperfusion lung injury may develop as a consequence of several pulmonary disorders such as lung transplantation. Gastric aspiration occurs frequently in several conditions such as anesthesia, trauma and pregnancy. The ventilator-induced ALI has been attributed to the deleterious effects on capillary stress due to alveolar overdistension. In experimental studies, PMA and oleic acid have been employed to induce ALI.

The pathogenesis of ALI/ARDS is complex. Experimental studies and clinical investigations from our and other laboratories have indicated the detrimental role of NO through the iNOS. Activation and recruitment of neutrophils that lead to release of neutrophil elastase, myeloperoxidase, malondialdehyde and proinflammatory cytokines may play an initial role in the pathogenesis of ALI/ARDS.

The possible therapeutic regimen for ALI/ARDS include extracorporeal membrane oxygenation, prone position, fluid and hemodynamic management and permissive hypercapnic acidosis *etc*. Other pharmacological treatments are anti-inflammatory and/or antimicrobial agents, inhalation of NO, glucocorticoids, surfactant therapy and agents that facilitate lung water resolution and ion transports. Adrenergic β agonists are able to accelerate lung fluid and ion removal and to stimulate surfactant secretion. There are reports on the actions of vascular endothelial growth factor and related molecules as well as angiotensin-converting enzyme.

Our laboratory has reported experimental studies on the effectiveness of several regimen for ALI/ARDS. In conscious rats, regular exercise training alleviates the endotoxin-induced ALI. Propofol and N-acetylcysteine exert protective effect on the ALI caused by endotoxin, oleic acid and PMA. We have also provided evidence that insulin possesses anti-inflammatory effect. Pentobarbital is capable of reducing the endotoxin-induced ALI and associated changes. In addition, nicotinamide or niacinamide (soluble B complex) abrogates the ALI caused by ischemia/reperfusion or endotoxemia. These nonpharmacological and pharmacological therapeutic strategies require further investigations for clinical application.

REFERENCES

1 **Ware LB**, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1334-1349
2 **Vincent JL**, Sakr Y, Ranieri VM. Epidemiology and outcome of acute respiratory failure in intensive care unit patients. *Crit Care Med* 2003; **31**: S296-S299
3 **Chen HI**, Kao SJ, Wang D, Lee RP, Su CF. Acute respiratory distress syndrome. *J Biomed Sci* 2003; **10**: 588-592
4 **Ksiazek TG**, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, Tong S, Urbani C, Comer JA, Lim W, Rollin PE, Dowell SF, Ling AE, Humphrey CD, Shieh WJ, Guarner J, Paddock CD, Rota P, Fields B, DeRisi J, Yang JY, Cox N, Hughes JM, LeDuc JW, Bellini WJ, Anderson LJ. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; **348**: 1953-1966
5 **Drosten C**, Günther S, Preiser W, van der Werf S, Brodt HR, Becker S, Rabenau H, Panning M, Kolesnikova L, Fouchier RA, Berger A, Burguière AM, Cinatl J, Eickmann M, Escriou N, Grywna K, Kramme S, Manuguerra JC, Müller S, Rickerts V, Stürmer M, Vieth S, Klenk HD, Osterhaus AD, Schmitz H, Doerr HW. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003; **348**: 1967-1976
6 **Lee N**, Hui D, Wu A, Chan P, Cameron P, Joynt GM, Ahuja A, Yung MY, Leung CB, To KF, Lui SF, Szeto CC, Chung S, Sung JJ. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003; **348**: 1986-1994
7 **Eisenhut M**, Wallace H, Barton P, Gaillard E, Newland P, Diver M, Southern KW. Pulmonary edema in meningococcal septicemia associated with reduced epithelial chloride transport. *Pediatr Crit Care Med* 2006; **7**: 119-124
8 **Kao SJ**, Yang FL, Hsu YH, Chen HI. Mechanism of fulminant pulmonary edema caused by enterovirus 71. *Clin Infect Dis* 2004; **38**: 1784-1788
9 **Kao SJ**, Wang D, Yeh DY, Hsu K, Hsu YH, Chen HI. Static inflation attenuates ischemia/reperfusion injury in an isolated rat lung in situ. *Chest* 2004; **126**: 552-558
10 **Kao SJ**, Yeh DY, Chen HI. Clinical and pathological features of fat embolism with acute respiratory distress syndrome. *Clin Sci* (Lond) 2007; **113**: 279-285
11 **Jian MY**, Koizumi T, Kubo K. Effects of nitric oxide synthase inhibitor on acid aspiration-induced lung injury in rats. *Pulm Pharmacol Ther* 2005; **18**: 33-39
12 **Chen HI**, Chang HR, Wu CY, Kao SJ, Wang D, Hsieh NK, Hsu YH. Nitric oxide in the cardiovascular and pulmonary circulation--a brief review of literatures and historical landmarks. *Chin J Physiol* 2007; **50**: 43-50
13 **Chen HI**, Kao SJ, Hsu YH. Pathophysiological mechanism of lung injury in patients with leptospirosis. *Pathology* 2007; **39**: 339-344
14 **Chen HI**, Sun SC, Chai CY. Pulmonary edema and hemorrhage resulting from cerebral compression. *Am J Physiol* 1973; **224**: 223-229
15 **Chen HI**, Chai CY. Pulmonary adema and hemorrhage as a consequence of systemic vasoconstriction. *Am J Physiol* 1974; **227**: 144-151

16 **Chen HI**. Hemodynamic mechanisms of neurogenic pulmonary edema. *Biol Signals* 1995; **4**: 186-192
17 **Chen HI**, Hu CT, Wu CY, Wang D. Nitric Oxide in Systemic and Pulmonary Hypertension. *J Biomed Sci* 1997; **4**: 244-248
18 **Chen HI**, Su CF, Chai CY. [Neural and hemodynamic mechanisms of neurogenic pulmonary edema]. *Sheng Li Ke Xue Jin Zhan* 1999; **30**: 203-206
19 **Ashbaugh DG**, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319-323
20 **Petty TL**, Ashbaugh DG. The adult respiratory distress syndrome. Clinical features, factors influencing prognosis and principles of management. *Chest* 1971; **60**: 233-239
21 **Murray JF**, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; **138**: 720-723
22 **Bernard GR**, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**: 818-824
23 **Weisman SJ**. Edema and congestion of the lungs resulting from intracranial hemorrhage. *Surgery* 1939; **6**: 722-729
24 **Campbell GS**, Visscher MB. Pulmonary lesions in guinea pigs with increased intracranial pressure, and the effect of bilateral cervical vagotomy. *Am J Physiol* 1949; **157**: 130-134
25 **Richards P**. Pulmonary oedema and intracranial lesions. *Br Med J* 1963; **2**: 83-86
26 **Ducker TB**. Increased intracranial pressure and pulmonary edema. 1. Clinical study of 11 patients. *J Neurosurg* 1968; **28**: 112-117
27 **Ducker TB**, Simmons RL. Increased intracranial pressure and pulmonary edema. 2. The hemodynamic response of dogs and monkeys to increased intracranial pressure. *J Neurosurg* 1968; **28**: 118-123
28 **Matthay MA**, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. *Am J Respir Cell Mol Biol* 2005; **33**: 319-327
29 **Bernard GR**. Acute respiratory distress syndrome: a historical perspective. *Am J Respir Crit Care Med* 2005; **172**: 798-806
30 **Ware LB**. Clinical Year in Review III: asthma, lung transplantation, cystic fibrosis, acute respiratory distress syndrome. *Proc Am Thorac Soc* 2007; **4**: 489-493
31 **Cushing H**. Concerning a definite regulatory mechanism of the vasomotor center which controls blood pressure during cerebral compression. *Bull Johns Hopkins Hosp* 1901; **12**: 290-292
32 **Cushing H**. Some experimental and clinical observations concerning states of increased intracranial pressure. *Am J Med Sci* 1902; **124**: 375-400
33 **Brashear RE**, Ross JC. Hemodynamic effects of elevated cerebrospinal fluid pressure: alterations with adrenergic blockade. *J Clin Invest* 1970; **49**: 1324-1333
34 **Burch GE**, Colcolough H, Giles T. Intracranial lesions and the heart. *Am Heart J* 1970; **80**: 574-575
35 **Chen HI**, Wang DJ. Systemic and pulmonary hemodynamic responses to intracranial hypertension. *Am J Physiol* 1984; **247**: H715-H721
36 **Su CF**, Hu CT, Chen HI. Effects of intracranial hypertension on steady and pulsatile haemodynamics in dogs. *Clin Exp Pharmacol Physiol* 1999; **26**: 898-902
37 **Su CF**, Yang YL, Lee MC, Chen HI. A severe vicious cycle in uncontrolled subarachnoid hemorrhage: the effects on cerebral blood flow and hemodynamic responses upon intracranial hypertension. *Chin J Physiol* 2006; **49**: 56-63
38 **Su CF**, Kuo TB, Kuo JS, Lai HY, Chen HI. Sympathetic and parasympathetic activities evaluated by heart-rate variability in head injury of various severities. *Clin Neurophysiol* 2005; **116**: 1273-1279
39 **Malik AB**. Mechanisms of neurogenic pulmonary edema. *Circ Res* 1985; **57**: 1-18
40 **Chen HI**, Chai CY. Circulatory and pulmonary segualae in hypertensive crisis-An animal study with intracranial hypertension. In: MRC (RSA)-NSC (ROC) Symposium on Hypertension, 1988: 11 (Abstract)
41 **Simon RP**. Neurogenic pulmonary edema. *Neurol Clin* 1993; **11**: 309-323
42 **Jourdan C**, Convert J, Rousselle C, Wasylkiewicz J, Mircevski V, Mottolese C, Lapras C. [Hemodynamic study of acute neurogenic pulmonary edema in children]. *Pediatrie* 1993; **48**: 805-812
43 **Campbell GS**, Haddy FJ. Circulatory changes and pulmonary lesions in dogs following increased intracranial pressure, and the effect of atropine upon such changes. *Am J Physiol* 1949; **158**: 96-102
44 **Simmons RL**, Ducker TB, Anderson RW. Pathogenesis of pulmonary edema following head trauma. An experimental study. *J Trauma* 1968; **8**: 800-811
45 **Bean JW**, Beckman DL. Centrogenic pulmonary pathology in mechanical head injury. *J Appl Physiol* 1969; **27**: 807-812
46 **Maire FW**, Patton HD. Neural structures involved in the genesis of preoptic pulmonary edema, gastric erosions and behavior changes. *Am J Physiol* 1956; **184**: 345-350
47 **Chen HI**, Liao JF, Kuo L, Ho ST. Centrogenic pulmonary hemorrhagic edema induced by cerebral compression in rats. Mechanism of volume and pressure loading in the pulmonary circulation. *Circ Res* 1980; **47**: 366-373
48 **Chen HI**, Shih WJ, Chen TP. A scintiphotographic study of pulmonary edema and hemorrhage induced by cerebral compression and norepinephrine. *Chin J Physiol* 1976; **22**: 65-72
49 **Chen HI**, Lin JD, Liao JF. Participation of regional sympathetic outflows in the centrogenic pulmonary pathology. *Am J Physiol* 1981; **240**: H109-H115
50 **Chen HI**, Wang YC, Chai CY. The Cushing responses in the systemic and pulmonary circulation: the role of adrenal glands, bronchial circulation and pulmonary innervation. *Chin J Physiol* 1987; **30**: 29-43
51 **Wang D**, Chou CL, Hsu K, Chen HI. Cyclooxygenase pathway mediates lung injury induced by phorbol and platelets. *J Appl Physiol* 1991; **70**: 2417-2421
52 **Wang D**, Li MH, Hsu K, Shen CY, Chen HI, Lin YC. Air embolism-induced lung injury in isolated rat lungs. *J Appl Physiol* 1992; **72**: 1235-1242
53 **Hsu K**, Wang D, Wu SY, Shen CY, Chen HI. Ischemia-reperfusion lung injury attenuated by ATP-MgCl2 in rats. *J Appl Physiol* 1994; **76**: 545-552
54 **Wang D**, Hsu K, Hwang CP, Chen HI. Measurement of nitric oxide release in the isolated perfused rat lung. *Biochem Biophys Res Commun* 1995; **208**: 1016-1020
55 **Hsu K**, Wang D, Chang ML, Wu CP, Chen HI. Pulmonary edema induced by phorbol myristate acetate is attenuated by compounds that increase intracellular cAMP. *Res Exp Med* (Berl) 1996; **196**: 17-28
56 **Wang D**, Wei J, Hsu K, Jau J, Lieu MW, Chao TJ, Chen HI. Effects of nitric oxide synthase inhibitors on systemic hypotension, cytokines and inducible nitric oxide synthase expression and lung injury following endotoxin administration in rats. *J Biomed Sci* 1999; **6**: 28-35
57 **Kao SJ**, Wei J, Hwang CP, Lieu MW, Jiang JS, Wang D, Chen HI. Modulatory effect of blood cells on hypoxic vasoconstriction response and nitric oxide release in rat lungs. *J Formos Med Assoc* 1999; **98**: 39-44
58 **Lee RP**, Wang D, Kao SJ, Chen HI. The lung is the major site that produces nitric oxide to induce acute pulmonary oedema in endotoxin shock. *Clin Exp Pharmacol Physiol* 2001; **28**: 315-320
59 **Huang KL**, Shaw KP, Wang D, Hsu K, Huang TS, Chen HI. Free radicals mediate amphetamine-induced acute pulmonary edema in isolated rat lung. *Life Sci* 2002; **71**: 1237-1244

60 **Lin HI**, Chu SJ, Wang D, Chen HI, Hsu K. Effects of an endogenous nitric oxide synthase inhibitor on phorbol myristate acetate-induced acute lung injury in rats. *Clin Exp Pharmacol Physiol* 2003; **30**: 393-398
61 **Kao SJ**, Peng TC, Lee RP, Hsu K, Chen CF, Hung YK, Wang D, Chen HI. Nitric oxide mediates lung injury induced by ischemia-reperfusion in rats. *J Biomed Sci* 2003; **10**: 58-64
62 **Chen HI**, Yeh DY, Liou HL, Kao SJ. Insulin attenuates endotoxin-induced acute lung injury in conscious rats. *Crit Care Med* 2006; **34**: 758-764
63 **Kao SJ**, Wang D, Lin HI, Chen HI. N-acetylcysteine abrogates acute lung injury induced by endotoxin. *Clin Exp Pharmacol Physiol* 2006; **33**: 33-40
64 **Chen HI**, Hsieh SY, Yang FL, Hsu YH, Lin CC. Exercise training attenuates septic responses in conscious rats. *Med Sci Sports Exerc* 2007; **39**: 435-442
65 **Su CF**, Yang FL, Chen HI. Inhibition of inducible nitric oxide synthase attenuates acute endotoxin-induced lung injury in rats. *Clin Exp Pharmacol Physiol* 2007; **34**: 339-346
66 **Kao SJ**, Su CF, Liu DD, Chen HI. Endotoxin-induced acute lung injury and organ dysfunction are attenuated by pentobarbital anaesthesia. *Clin Exp Pharmacol Physiol* 2007; **34**: 480-487
67 **Su CF**, Liu DD, Kao SJ, Chen HI. Nicotinamide abrogates acute lung injury caused by ischaemia/reperfusion. *Eur Respir J* 2007; **30**: 199-204
68 **Chu CH**, David Liu D, Hsu YH, Lee KC, Chen HI. Propofol exerts protective effects on the acute lung injury induced by endotoxin in rats. *Pulm Pharmacol Ther* 2007; **20**: 503-512
69 **Chuang IC**, Liu DD, Kao SJ, Chen HI. N-acetylcysteine attenuates the acute lung injury caused by phorbol myristate acetate in isolated rat lungs. *Pulm Pharmacol Ther* 2007; **20**: 726-733
70 **Liu DD**, Hsu YH, Chen HI. Endotoxin-induced acute lung injury is enhanced in rats with spontaneous hypertension. *Clin Exp Pharmacol Physiol* 2007; **34**: 61-69
71 **Liu YC**, Kao SJ, Chuang IC, Chen HI. Nitric oxide modulates air embolism-induced lung injury in rats with normotension and hypertension. *Clin Exp Pharmacol Physiol* 2007; **34**: 1173-1180
72 **Kao SJ**, Liu DD, Su CF, Chen HI. Niacinamide abrogates the organ dysfunction and acute lung injury caused by endotoxin. *J Cardiovasc Pharmacol* 2007; **50**: 333-342
73 **Moncada S**, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 1991; **43**: 109-142
74 **Chen HI**, Hu CT. Endogenous nitric oxide on arterial hemodynamics: a comparison between normotensive and hypertensive rats. *Am J Physiol* 1997; **273**: H1816-H1823
75 **Hu CT**, Chang KC, Wu CY, Chen HI. Acute effects of nitric oxide blockade with L-NAME on arterial haemodynamics in the rat. *Br J Pharmacol* 1997; **122**: 1237-1243
76 **Bone RC**, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest* 1997; **112**: 235-243
77 **Parrillo JE**. Pathogenetic mechanisms of septic shock. *N Engl J Med* 1993; **328**: 1471-1477
78 **Wheeler AP**, Bernard GR. Treating patients with severe sepsis. *N Engl J Med* 1999; **340**: 207-214
79 **Szabó C**, Mitchell JA, Thiemermann C, Vane JR. Nitric oxide-mediated hyporeactivity to noradrenaline precedes the induction of nitric oxide synthase in endotoxin shock. *Br J Pharmacol* 1993; **108**: 786-792
80 **Hsu YH**, Kao SJ, Lee RP, Chen HI. Acute pulmonary oedema: rare causes and possible mechanisms. *Clin Sci* (Lond) 2003; **104**: 259-264
81 **Hsu YH**, Chen HI. The involvement of nitric oxide and beta-adrenergic pathway signalling in pulmonary oedema and fluid clearance. *Pathology* 2007; **39**: 612-613
82 **Hsu YH**, Chen HI. Pulmonary pathology in patients associated with scrub typhus. *Pathology* 2008; **40**: 268-271
83 **Hsu YH**, Chen HI. Acute respiratory distress syndrome associated with rabies. *Pathology* 2008; **40**: 647-650
84 **Holmes F**, Harlan J, Felt S, Ruhlen J, Murphy B. Letter: Pulmonary oedema in hypercalcaemic crisis. *Lancet* 1974; **1**: 311-312
85 **Chen HI**, Yeh DY, Kao SJ. The detrimental role of inducible nitric oxide synthase in the pulmonary edema caused by hypercalcemia in conscious rats and isolated lungs. *J Biomed Sci* 2008; **15**: 227-238
86 **Ischiropoulos H**, Mendiguren I, Fisher D, Fisher AB, Thom SR. Role of neutrophils and nitric oxide in lung alveolar injury from smoke inhalation. *Am J Respir Crit Care Med* 1994; **150**: 337-341
87 **Hinder F**, Meyer J, Booke M, Ehardt JS, Salsbury JR, Traber LD, Traber DL. Endogenous nitric oxide and the pulmonary microvasculature in healthy sheep and during systemic inflammation. *Am J Respir Crit Care Med* 1998; **157**: 1542-1549
88 **Kristof AS**, Goldberg P, Laubach V, Hussain SN. Role of inducible nitric oxide synthase in endotoxin-induced acute lung injury. *Am J Respir Crit Care Med* 1998; **158**: 1883-1889
89 **Evgenov OV**, Hevroy O, Bremnes KE, Bjertnaes LJ. Effect of aminoguanidine on lung fluid filtration after endotoxin in awake sheep. *Am J Respir Crit Care Med* 2000; **162**: 465-470
90 **Inoue H**, Aizawa H, Nakano H, Matsumoto K, Kuwano K, Nadel JA, Hara N. Nitric oxide synthase inhibitors attenuate ozone-induced airway inflammation in guinea pigs. Possible role of interleukin-8. *Am J Respir Crit Care Med* 2000; **161**: 249-256
91 **Cuzzocrea S**, Mazzon E, Calabro G, Dugo L, De Sarro A, van De LOO FA, Caputi AP. Inducible nitric oxide synthase-knockout mice exhibit resistance to pleurisy and lung injury caused by carrageenan. *Am J Respir Crit Care Med* 2000; **162**: 1859-1866
92 **Wang le F**, Patel M, Razavi HM, Weicker S, Joseph MG, McCormack DG, Mehta S. Role of inducible nitric oxide synthase in pulmonary microvascular protein leak in murine sepsis. *Am J Respir Crit Care Med* 2002; **165**: 1634-1639
93 **Agorreta J**, Garayoa M, Montuenga LM, Zulueta JJ. Effects of acute hypoxia and lipopolysaccharide on nitric oxide synthase-2 expression in acute lung injury. *Am J Respir Crit Care Med* 2003; **168**: 287-296
94 **Razavi HM**, Wang le F, Weicker S, Rohan M, Law C, McCormack DG, Mehta S. Pulmonary neutrophil infiltration in murine sepsis: role of inducible nitric oxide synthase. *Am J Respir Crit Care Med* 2004; **170**: 227-233
95 **Hesse AK**, Dörger M, Kupatt C, Krombach F. Proinflammatory role of inducible nitric oxide synthase in acute hyperoxic lung injury. *Respir Res* 2004; **5**: 11
96 **Genovese T**, Cuzzocrea S, Di Paola R, Failla M, Mazzon E, Sortino MA, Frasca G, Gili E, Crimi N, Caputi AP, Vancheri C. Inhibition or knock out of inducible nitric oxide synthase result in resistance to bleomycin-induced lung injury. *Respir Res* 2005; **6**: 58
97 **Kao SJ**, Chen HI. Nitric oxide mediates acute lung injury caused by fat embolism in isolated rat's lungs. *J Trauma* 2008; **64**: 462-469
98 **Liu DD**, Kao SJ, Chen HI. N-acetylcysteine attenuates acute lung injury induced by fat embolism. *Crit Care Med* 2008; **36**: 565-571
99 **Chen HI**, Hsieh NK, Kao SJ, Su CF. Protective effects of propofol on acute lung injury induced by oleic acid in conscious rats. *Crit Care Med* 2008; **36**: 1214-1221
100 **Yang YL**, Huang KL, Liou HL, Chen HI. The involvement of nitric oxide, nitric oxide synthase, neutrophil elastase, myeloperoxidase and proinflammatory cytokines in the acute lung injury caused by phorbol myristate acetate. *J Biomed Sci* 2008; **15**: 499-507
101 **Lin NT**, Yang FL, Lee RP, Peng TC, Chen HI. Inducible nitric oxide synthase mediates cytokine release: the time course in conscious and septic rats. *Life Sci* 2006; **78**: 1038-1043

102 **Lee RP**, Wang D, Lin NT, Chen HI. Physiological and chemical indicators for early and late stages of sepsis in conscious rats. *J Biomed Sci* 2002; **9**: 613-621
103 **Fabian TC**. Unravelling the fat embolism syndrome. *N Engl J Med* 1993; **329**: 961-963
104 **Goldhaber SZ**. Pulmonary embolism. *Lancet* 2004; **363**: 1295-1305
105 **Sleiman C**, Mal H, Fournier M, Duchatelle JP, Icard P, Groussard O, Jebrak G, Mollo JL, Raffy O, Roue C. Pulmonary reimplantation response in single-lung transplantation. *Eur Respir J* 1995; **8**: 5-9
106 **Levinson RM**, Shure D, Moser KM. Reperfusion pulmonary edema after pulmonary artery thromboendarterectomy. *Am Rev Respir Dis* 1986; **134**: 1241-1245
107 **Ward BJ**, Pearse DB. Reperfusion pulmonary edema after thrombolytic therapy of massive pulmonary embolism. *Am Rev Respir Dis* 1988; **138**: 1308-1311
108 **Marik PE**. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med* 2001; **344**: 665-671
109 **Olsson GL**, Hallen B, Hambraeus-Jonzon K. Aspiration during anaesthesia: a computer-aided study of 185,358 anaesthetics. *Acta Anaesthesiol Scand* 1986; **30**: 84-92
110 **Warner MA**, Warner ME, Weber JG. Clinical significance of pulmonary aspiration during the perioperative period. *Anesthesiology* 1993; **78**: 56-62
111 **Milberg JA**, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983-1993. *JAMA* 1995; **273**: 306-309
112 **Zilberberg MD**, Epstein SK. Acute lung injury in the medical ICU: comorbid conditions, age, etiology, and hospital outcome. *Am J Respir Crit Care Med* 1998; **157**: 1159-1164
113 **Safdar Z**, Yiming M, Grunig G, Bhattacharya J. Inhibition of acid-induced lung injury by hyperosmolar sucrose in rats. *Am J Respir Crit Care Med* 2005; **172**: 1002-1007
114 **Davidson BA**, Knight PR, Wang Z, Chess PR, Holm BA, Russo TA, Hutson A, Notter RH. Surfactant alterations in acute inflammatory lung injury from aspiration of acid and gastric particulates. *Am J Physiol Lung Cell Mol Physiol* 2005; **288**: L699-L708
115 **Brackenbury AM**, Puligandla PS, McCaig LA, Nikore V, Yao LJ, Veldhuizen RA, Lewis JF. Evaluation of exogenous surfactant in HCL-induced lung injury. *Am J Respir Crit Care Med* 2001; **163**: 1135-1142
116 **Vadász I**, Morty RE, Kohstall MG, Olschewski A, Grimminger F, Seeger W, Ghofrani HA. Oleic acid inhibits alveolar fluid reabsorption: a role in acute respiratory distress syndrome? *Am J Respir Crit Care Med* 2005; **171**: 469-479
117 **de Abreu MG**, Quelhas AD, Spieth P, Bräuer G, Knels L, Kasper M, Pino AV, Bleyl JU, Hübler M, Bozza F, Salluh J, Kuhlisch E, Giannella-Neto A, Koch T. Comparative effects of vaporized perfluorohexane and partial liquid ventilation in oleic acid-induced lung injury. *Anesthesiology* 2006; **104**: 278-289
118 **Chu SJ**, Chang DM, Wang D, Hsu K, Chiang CH. Protective effect of lipophilic antioxidants on phorbol-induced acute lung injury in rats. *Crit Care Med* 2001; **29**: 819-824
119 **Creamer KM**, McCloud LL, Fisher LE, Ehrhart IC. Pentoxifylline rescue preserves lung function in isolated canine lungs injured with phorbol myristate acetate. *Chest* 2001; **119**: 1893-1900
120 **Kuraki T**, Ishibashi M, Takayama M, Shiraishi M, Yoshida M. A novel oral neutrophil elastase inhibitor (ONO-6818) inhibits human neutrophil elastase-induced emphysema in rats. *Am J Respir Crit Care Med* 2002; **166**: 496-500
121 **Koshika T**, Ishizaka A, Nagatomi I, Sudo Y, Hasegawa N, Goto T. Pretreatment with FK506 improves survival rate and gas exchange in canine model of acute lung injury. *Am J Respir Crit Care Med* 2001; **163**: 79-84
122 **Murakami K**, Cox RA, Hawkins HK, Schmalstieg FC, McGuire RW, Jodoin JM, Traber LD, Traber DL. Cepharanthin, an alkaloid from Stephania cepharantha, inhibits increased pulmonary vascular permeability in an ovine model of sepsis. *Shock* 2003; **20**: 46-51
123 **Kinoshita M**, Ono S, Mochizuki H. Neutrophils mediate acute lung injury in rabbits: role of neutrophil elastase. *Eur Surg Res* 2000; **32**: 337-346
124 **Abraham E**. Neutrophils and acute lung injury. *Crit Care Med* 2003; **31**: S195-S199
125 **Bursten SL**, Federighi DA, Parsons P, Harris WE, Abraham E, Moore EE, Moore FA, Bianco JA, Singer JW, Repine JE. An increase in serum C18 unsaturated free fatty acids as a predictor of the development of acute respiratory distress syndrome. *Crit Care Med* 1996; **24**: 1129-1136
126 **Quinlan GJ**, Lamb NJ, Evans TW, Gutteridge JM. Plasma fatty acid changes and increased lipid peroxidation in patients with adult respiratory distress syndrome. *Crit Care Med* 1996; **24**: 241-246
127 **Schmidt R**, Meier U, Yabut-Perez M, Walmrath D, Grimminger F, Seeger W, Günther A. Alteration of fatty acid profiles in different pulmonary surfactant phospholipids in acute respiratory distress syndrome and severe pneumonia. *Am J Respir Crit Care Med* 2001; **163**: 95-100
128 **Günther A**, Schmidt R, Harodt J, Schmehl T, Walmrath D, Ruppert C, Grimminger F, Seeger W. Bronchoscopic administration of bovine natural surfactant in ARDS and septic shock: impact on biophysical and biochemical surfactant properties. *Eur Respir J* 2002; **19**: 797-804
129 **Pratt PC**, Vollmer RT, Shelburne JD, Crapo JD. Pulmonary morphology in a multihospital collaborative extracorporeal membrane oxygenation project. I. Light microscopy. *Am J Pathol* 1979; **95**: 191-214
130 **Ricard JD**, Dreyfuss D, Saumon G. Ventilator-induced lung injury. *Eur Respir J Suppl* 2003; **42**: 2s-9s
131 **Vlahakis NE**, Hubmayr RD. Cellular stress failure in ventilator-injured lungs. *Am J Respir Crit Care Med* 2005; **171**: 1328-1342
132 **Piantadosi CA**, Schwartz DA. The acute respiratory distress syndrome. *Ann Intern Med* 2004; **141**: 460-470
133 **Lee WL**, Downey GP. Leukocyte elastase: physiological functions and role in acute lung injury. *Am J Respir Crit Care Med* 2001; **164**: 896-904
134 **Yoshimura K**, Nakagawa S, Koyama S, Kobayashi T, Homma T. Roles of neutrophil elastase and superoxide anion in leukotriene B4-induced lung injury in rabbit. *J Appl Physiol* 1994; **76**: 91-96
135 **Puneet P**, Moochhala S, Bhatia M. Chemokines in acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol* 2005; **288**: L3-L15
136 **Fan J**, Ye RD, Malik AB. Transcriptional mechanisms of acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2001; **281**: L1037-L1050
137 **Sartori C**, Matthay MA. Alveolar epithelial fluid transport in acute lung injury: new insights. *Eur Respir J* 2002; **20**: 1299-1313
138 **Mutlu GM**, Sznajder JI. Mechanisms of pulmonary edema clearance. *Am J Physiol Lung Cell Mol Physiol* 2005; **289**: L685-L695
139 **Hubmayr RD**. Perspective on lung injury and recruitment: a skeptical look at the opening and collapse story. *Am J Respir Crit Care Med* 2002; **165**: 1647-1653
140 **Angus D**, Ishizaka A, Matthay M, Lemaire F, Macnee W, Abraham E. Critical care in AJRCCM 2004. *Am J Respir Crit Care Med* 2005; **171**: 537-544
141 **Mols G**, Priebe HJ, Guttmann J. Alveolar recruitment in acute lung injury. *Br J Anaesth* 2006; **96**: 156-166
142 **Galiatsou E**, Kostanti E, Svarna E, Kitsakos A, Koulouras V, Efremidis SC, Nakos G. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. *Am J Respir Crit Care Med* 2006; **174**: 187-197
143 **Laffey JG**, Honan D, Hopkins N, Hyvelin JM, Boylan JF,

McLoughlin P. Hypercapnic acidosis attenuates endotoxin-induced acute lung injury. *Am J Respir Crit Care Med* 2004; **169**: 46-56
144 **Broccard AF**, Hotchkiss JR, Vannay C, Markert M, Sauty A, Feihl F, Schaller MD. Protective effects of hypercapnic acidosis on ventilator-induced lung injury. *Am J Respir Crit Care Med* 2001; **164**: 802-806
145 **Ni Chonghaile M**, Higgins B, Laffey JG. Permissive hypercapnia: role in protective lung ventilatory strategies. *Curr Opin Crit Care* 2005; **11**: 56-62
146 **Alsaghir AH**, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med* 2008; **36**: 603-609
147 **Lang JD**, Figueroa M, Sanders KD, Aslan M, Liu Y, Chumley P, Freeman BA. Hypercapnia via reduced rate and tidal volume contributes to lipopolysaccharide-induced lung injury. *Am J Respir Crit Care Med* 2005; **171**: 147-157
148 **Feihl F**, Eckert P, Brimioulle S, Jacobs O, Schaller MD, Mélot C, Naeije R. Permissive hypercapnia impairs pulmonary gas exchange in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2000; **162**: 209-215
149 **Calfee CS**, Matthay MA. Nonventilatory treatments for acute lung injury and ARDS. *Chest* 2007; **131**: 913-920
150 **Fan E**, Needham DM, Stewart TE. Ventilatory management of acute lung injury and acute respiratory distress syndrome. *JAMA* 2005; **294**: 2889-2896
151 **Hite RD**, Morris PE. Acute respiratory distress syndrome: pharmacological treatment options in development. *Drugs* 2001; **61**: 897-907
152 **Brower RG**, Ware LB, Berthiaume Y, Matthay MA. Treatment of ARDS. *Chest* 2001; **120**: 1347-1367
153 **Moloney ED**, Evans TW. Pathophysiology and pharmacological treatment of pulmonary hypertension in acute respiratory distress syndrome. *Eur Respir J* 2003; **21**: 720-727
154 **Griffiths MJ**, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005; **353**: 2683-2695
155 **Mura M**, dos Santos CC, Stewart D, Liu M. Vascular endothelial growth factor and related molecules in acute lung injury. *J Appl Physiol* 2004; **97**: 1605-1617
156 **Imai Y**, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005; **436**: 112-116
157 **Aitkenhead AR**, Pepperman ML, Willatts SM, Coates PD, Park GR, Bodenham AR, Collins CH, Smith MB, Ledingham IM, Wallace PG. Comparison of propofol and midazolam for sedation in critically ill patients. *Lancet* 1989; **2**: 704-709
158 **Bryson HM**, Fulton BR, Faulds D. Propofol. An update of its use in anaesthesia and conscious sedation. *Drugs* 1995; **50**: 513-559
159 **Yang FL**, Li CH, Hsu BG, Tsai NM, Lin SZ, Harn HJ, Chen HI, Liao KW, Lee RP. The reduction of tumor necrosis factor-alpha release and tissue damage by pentobarbital in the experimental endotoxemia model. *Shock* 2007; **28**: 309-316
160 **Hsu BG**, Yang FL, Lee RP, Peng TC, Harn HJ, Chen HI. N-acetylcysteine ameliorates lipopolysaccharide-induced organ damage in conscious rats. *J Biomed Sci* 2004; **11**: 152-162
161 **Hsu BG**, Lee RP, Yang FL, Harn HJ, Chen HI. Post-treatment with N-acetylcysteine ameliorates endotoxin shock-induced organ damage in conscious rats. *Life Sci* 2006; **79**: 2010-2016
162 **Molnár Z**, Shearer E, Lowe D. N-Acetylcysteine treatment to prevent the progression of multisystem organ failure: a prospective, randomized, placebo-controlled study. *Crit Care Med* 1999; **27**: 1100-1104
163 **Berger MM**, Chioléro RL. Antioxidant supplementation in sepsis and systemic inflammatory response syndrome. *Crit Care Med* 2007; **35**: S584-S590
164 **Molnár Z**. N-acetylcysteine as the magic bullet: too good to be true. *Crit Care Med* 2008; **36**: 645-646

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Events Calendar 2012

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41st Critical Care Congress
Society of Critical Care Medicine
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12th Annual International Symposium on Congenital Heart Disease
St. Petersburg, FL, United States

February 26-29, 2012
11th International Dead Sea Symposium on Cardiac Arrhythmias and Device Therapy
International Convention Center,
Jerusalem, Israel

March 2-3, 2012
Twelfth Annual John M Templeton Jr Pediatric Trauma Symposium
Philadelphia, PA, United States

March 25-30, 2012
5th World Congress of Anaesthesiologists
Buenos Aires, Argentina

April 11-13, 2012
Society of Trauma Nurses 2012 Annual Conference
Savannah, GA, United States

May 3-5, 2012
18th Annual Spring Meeting of the Anesthesia History Association
Kansas City, MI, United States

May 10-11, 2012
National Trauma Institute 2012 Annual Conference
San Antonio, TX, United States

May 18-23, 2012
American Thoracic Society 2012 International Conference
San Francisco, CA, United States

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European Society of Intensive Care Medicine Summer Conference: Trauma Update 2012
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June 28-29, 2012
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August 27-28, 2012
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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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