European Review for Medical and Pharmacological Sciences 2020; 24: 11374-11380

Effects of non-invasive ventilation on renal and endothelial function in patients with respiratory failure

S. LAI[1], S. MAZZAFERRO[1], A.P. MITTERHOFER[1], F. TINTI[1], A. GIOVANNETTI[2], C. CASELLA[3], A.M. PERROTTA[1], D. MASTROLUCA[1], A. GALANI[4], A. MARRA[5], A. MAZZARELLA[1], A. OLIVA[5], C.M. MASTROIANNI[5], P. PALANGE[5]

[1]Department of Translational and Precision Medicine, Unit of Nephrology, Sapienza University of Rome, Rome, Italy
[2]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy
[3]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy
[4]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[5]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

Abstract. – OBJECTIVE: Non-invasive positive pressure ventilation (NIV) is now an indispensable safeguard in the management of many pathologies. However, sometimes the positive end-expiratory pressure (PEEP) showed harmful effects on renal function, although effects on renal hemodynamic are unclear. We aimed at evaluating the effects of NIV on renal and endothelial function, in patients with chronic or acute respiratory failure.

PATIENTS AND METHODS: We performed a longitudinal, prospective, interventional study. We enrolled 17 hospitalized and non-hospitalized patients (11 males) with indication to NIV and stable hemodynamic parameters. Patients were treated with NIV and followed up at T0, at T1 (at the end of the NIV cycle) and at T2 (fifteen days after).

RESULTS: 17 patients (11 males) with a mean age of 71.94 ± 14.89 years were enrolled. A significant increase in flow mediated dilation (FMD) was found ($p = 0.004$). We showed a significant improvement, after NIV, in the values of pH ($p = 0.0002$), pCO2 (p = 0.0001), pO2 ($p = 0.04$), lactates ($p = 0.04$), sO2 ($p = 0.02$) and in the P/F Ratio ($p = 0.004$). We also showed a significant reduction of serum glucose ($p = 0.01$) and a significant increase of serum chlorine ($p = 0.047$), while we did not report a significant increase of creatinine ($p = 0.297$) or a significant change in diuresis.

CONCLUSIONS: In our study NIV has no significant effects on renal function in patients with respiratory failure. Probably these patients required low PEEP values, which were less harmful to lung parenchyma and not effective on systemic hemodynamic. Furthermore, NIV has improved endothelial function in the short term, likely by reducing oxidative stress, as improvements of the gas-analysis parameters showed. Therefore, NIV could help to reduce cardiovascular risk of patients improving endothelial function.

Key Words:
Non-invasive positive pressure ventilation, Positive end-expiratory pressure, Endothelial dysfunction, Renal function, Cardiovascular risk.

Abbreviations

Non-invasive positive pressure ventilation (NIV), positive end-expiratory pressure (PEEP), Chronic obstructive pulmonary disease (COPD), Acute kidney Injury (AKI), Chronic kidney disease-epidemiology formula (CKD-EPI),estimated glomerular filtration rate (eGFR), Flow-mediated dilation brachial artery (FMD), renal blood flow (RBF), Renal Resistive index (RRI), atrophy index (AI), antidiuretic hormone (ADH), nitric oxide (NO), ultrasonographic exams (US), arterial blood gas analysis (ABG).

Introduction

Chronic obstructive pulmonary disease (COPD) is responsible for early mortality, high death rates and huge health costs. COPD includes heterogeneous conditions all characterized by a not reversible (or partially reversible) ventilatory obstructive deficit[1]. Beyond pharmacotherapy, major treatment options are oxygen supplemen-

Corresponding Author: Silvia Lai, MD; e-mail address: silvia.lai@uniroma1.it

tation, pulmonary rehabilitation and mechanical ventilation; surgery may be considered in selected patients[2]. Exacerbations of COPD and acute or chronic respiratory failure cause a high rate of hospital admissions and mortality and they strongly influence quality of life. NIV is an assisted ventilation, like PEEP techniques, to keep the airways open, without a surgical or artificial access to the airways (e.g., tracheostomy tube or endotracheal tube). Long-term or sudden non-invasive positive pressure ventilation (NIV) leads to an improvement of clinical outcome. In patients with acute unbalanced hypercapnic exacerbations of COPD techniques without positive end-expiratory pressure (PEEP) are more efficient and cost-effective than others using PEEP[2,3]. Nowadays, NIV is preferable to invasive support by tracheostomy in the acute care hospital setting, for long term care and house management of patients requiring mechanical ventilation. Moreover, tracheostomy cares complicate management for both patients and caregivers, worsening patient's quality of life[4]. Recent animal models and clinical studies[5] have shown that PEEP ventilation can worse pre-existing lung injury and cause ventilator-induced lung injury, which has been linked with the development of systemic inflammation and multi organ dysfunction, including renal failure. Increased vascular stiffness, neuroendocrine activation, tissue hypoxia, oxidative stress and cellular activation are all involved in kidney damage. Barotrauma, triggered by PEEP techniques, can lead to the release of mediators responsible for Acute Kidney Injury (AKI). Moreover, right ventricular dysfunction and lung congestion could contribute to a reduction in renal perfusion, worsening the acid-base balance. Effects of mechanical ventilation on pulmonary and cardiovascular function have been extensively studied, while its effects on renal function are not well defined. Previous experimental studies and few clinical reports[6,7] have shown a significant effect of NIV on renal function. We aimed at evaluating the effects of NIV on renal and endothelial function, in patients with chronic or acute respiratory failure.

Patients and Methods

The study protocol was approved by the Local Clinical Research Ethics Committee. The study conforms to the principles outlined in the Declaration of Helsinki and we obtained a written informed consent. We performed a longitudinal, prospective and interventional study on 17 hospitalized and non-hospitalized patients (11 males) at the University Hospital "Policlinico Umberto I" of Rome (Sapienza University of Rome, Italy). Enrolled patients were treated with ventilatory assistance; some of them had already undergone ventilatory assistance. Patients were enrolled from January 2019 to October 2019. We checked out patients at T0 and T1 (at the end of the NIV cycle) and at T2 (fifteen days after the ventilation cycle). At T0 we performed hematochemical exams, arterial blood gas analysis (ABG) and ultrasonographic exams (US). At T1 we repeated ABG and US, while at T2 we only performed hematochemical exams.

Inclusion Criteria

Patients with indication to NIV without hemodynamic instability.

Patients aged >18 and <80 years old with estimated glomerular filtration rate (eGFR) > 30 ml/min.

Exclusion Criteria

Hemodynamic instability, ongoing sepsis, eGFR < 30 ml/min; patients who refused to give consent.

Laboratory Measurements

In all patients, levels of fasting plasma glucose (mg/dL), creatinine (mg/dL), serum nitrogen (mg/dL), serum uric acid (mg/dL), serum calcium (mg/dL), serum phosphorus (mg/dL), serum sodium (mg/dL), serum potassium (mg/dL), and serum chlorine (mg/dL) were measured using standard automated techniques. Arterial blood gas was performed using a blood gas analyzer (Nova Phox Plus C, Prospect Street, Waltham, MA 02454-9141, USA). The eGFR was calculated with the abbreviated Chronic kidney disease-epidemiology formula (CKD-EPI), as defined by Levey et al[8].

Flow-Mediated Dilation Brachial Artery (FMD)

According to the method described by Corretti et al[9], the endothelium-dependent vasodilation (FMD) of the brachial artery was assessed using a B-mode ultrasound machine Toshiba Aplio xV (Toshiba Aplio xV, Toshiba American Medical Systems, Inc., Tustin, CA, USA) equipped with a 5- to 12 MHz linear transducer, following a standardized protocol. Flow-mediated dilation was typically expressed as the change in

post-stimulus diameter as a percentage of the baseline diameter. FMD: (diameter post-hyperemia-basal diameter/basal diameter) x 100. The values of FMD were considered normal if they were greater than 10%.

Renal Resistive index (RRI)

Participants were studied with the high-resolution B-mode ultrasound machine Toshiba Aplio xV (Toshiba Aplio xV, Toshiba American Medical Systems, Inc., Tustin, CA, USA) equipped with a 3-3.5 MHz convex transducer. Renal resistive index (RRI) values were determined with the mean of three separate measurements in the renal superior pole, interpolar regional and inferior pole on the level of the interlobular, interlobar or arcuate arteries in both kidneys. We used anterior and oblique approach, to detect the renal arteries and intra-parenchymal vessels. Three to five reproducible and consecutive waveforms with similar aspect from each kidney were obtained. These measurements were used to calculate the average RRI value for each kidney, and then the average RRI value for each patient was calculated as the mean of the RRI in the left and right kidney[10]. We determined the peak systolic velocity and end-diastolic velocity (centimeters/second) to calculate the RRI as = [1-(end-diastolic velocity ÷ maximal systolic velocity)] x 100. The intra-reader correlation coefficient for RRI was 0.97, whereas the inter-reader was 0.92. We also assessed the atrophy index (AI)[11].

Statistical Analysis

Data management and analysis were performed using IBM® Statistical Package for Social Science (SPSS®) Statistics 22.0 for Windows® software (IBM Corporation, Armonk, NY, USA). The normality of variables was tested using the Shapiro-Wilk method for normal distributions. All continuous variables were expressed as mean ± standard deviation, categorical variables were expressed as number (percentage). We used the *t*-test for paired samples to study the variations of the indices of interest before and after the administration of non-invasive mechanical ventilation. A probability value of $p < 0.05$ was considered to be statistically significant.

Results

Patient's characteristics at T0 and at T2 are shown in Table I. A total of 17 patients (11 males) with a mean age of 71.94 ± 14.89 years were enrolled. A significant increase in FMD was found in patients treated with NIV ($p = 0.004$). There was no significant change in the RRI ($p = 0.655$) and in the AI ($p = 0.642$). Data showed a significant improvement, after NIV, in the values of pH ($p = 0.0002$), pCO2 ($p = 0.0001$), pO2 ($p = 0.04$), lactates ($p = 0.04$), sO2 ($p = 0.02$) and in the P/F Ratio ($p = 0.004$) (Figure 1). There was also a significant reduction of serum glucose ($p = 0.01$) and a significant increase of serum chlorine ($p = 0.047$). A significant increase in creatinine ($p = 0.297$) (Table I) or a significant change in diuresis are not shown. The correlations between the different parameters, assessed with Pearson tests, were not significant; therefore, we did not find a linear variation between the changes in arterial gases, FMD and RRI.

Table I. Patients' characteristics at T0 (baseline) and at T2 (fifteen days after the ventilation cycle).

Values	T0	T2	*p* value
Creatinine mg/dL	0.84 ± 0.27	0.79 ± 0.14	0.297
eGFR ml/min	88.0 ± 26.18	89.88 ± 17.65	0.732
Serum glucose mg/dL	190.04 ± 97.69	120.16 ± 44.90	0.013
Serum nitrogen mg/dL	35.69 ± 14.45	37.34 ± 12.80	0.710
Sodium mEq/L	142.0 ± 4.21	144.11 ± 3.29	0.127
Potassium mEq/L	4.14 ± 0.55	4.24 ± 0.65	0.621
Calcium mg/dL	8.94 ± 0.45	9.0 ± 0.65	0.588
Phosphorus mg/dL	4.48 ± 2.46	3.47 ± 0.98	0.180
Chlorine mEq/L	96.11 ±3.44	99.55 ± 3.60	0.047
Magnesium mg/dL	2.02 ± 0.10	2.17 ± 0.20	0.105
CRP µg/L	17493.33 ± 27550.72	17660.0 ± 25903.41	0.983

Data are show as mean ± standard deviation or number (%). *Abbreviations:* eGFR, estimated Glomerular Filtration Rate; CRP, C-Reactive Protein.

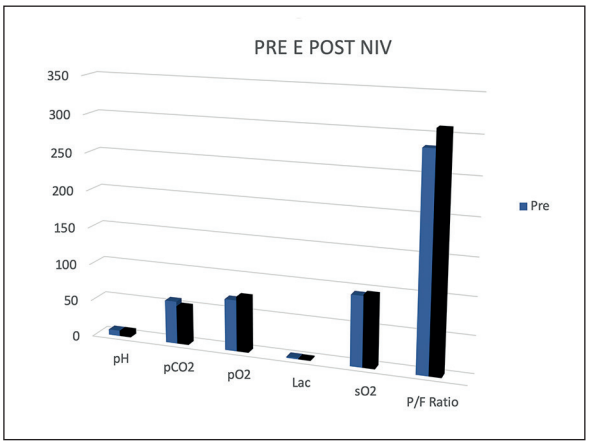

Figure 1. Patients' characteristics pre and post NIV. *Abbreviation:* NIV, Non invasive positive pressure ventilation.

Discussion

NIV is a benchmark in the management and therapy of several pathologies; however, PEEP has not always shown beneficial results on renal function. Some studies[6,7] suggested that renal dysfunction also has a direct, adverse effect on pulmonary function. In 1947, Drury et al[12] observed a sudden reduction in renal blood flow (RBF), eGFR and diuresis after the administration of NIV to their patients, measured with the clearance of inulin. Moreover, Gammanpila et al[13], Marquez et al[14] and Fewell et al[15] reported similar results on animal models. Human studies confirmed many of the observations made on animal models. Hemmer and Suter[16] analyzed the effects of high PEEP levels on 10 patients, similarly, demonstrating a reduction in diuresis and eGFR. All these changes were reversible with the suspension of PEEP. However, not all the studies performed on human models have led to the same observations. Jarnberg et al[17] observed a reduction in RBF and diuresis, without change in eGFR. Different mechanisms have been hypothesized causing kidney dysfunction. Ventilatory support causes cardiovascular remodeling through complex interactions between intrathoracic pressure, intravascular volume and heart performance. The positive intrathoracic pressure inhibits venous return, resulting in preload reduction. It also causes afterload increase, by squeezing pulmonary and mediastinal vessels. Therefore, a reduction in cardiac output is determined and it is responsible for decrease in renal perfusion[18]. Mullins et al[19], on canine models, showed that PEEP did not cause a significant modification of renal function, as long as correct renal perfusion was maintained. Evidence demonstrated how changes in pulmonary hemodynamics, during NIV, depend on intravascular volume and cardio-pulmonary status, explaining the contradictory results found in many studies. Hall et al[20] suggested that PEEP ventilation, by redistributing renal circulation from the cortex to the medulla through the release of vasoactive mediators, could depress renal function. Many hormonal responses to PEEP have been studied, including those of atrial natriuretic peptide, antidiuretic hormone, renin, aldosterone, prostaglandins, adrenaline and norepinephrine. The result of all these hormonal pathways is the decrease in RBF, a reduction of eGFR and saline retention with oliguria. Despite some conflicting data, fluid retention could be caused by the release of vasoactive mediators induced by NIV[21]. These mediators reverse intrarenal circulation from the cortex to the medulla[22]. The release of antidiuretic hormone (ADH) is likely multifactorial. Henry et al[23] suggests that the increased secretion of ADH is associated with the reduction in the stretching of cardiac muscle fibers, due to volume depletion. Many experiments involving denervation procedures just reduced the secretion of ADH, without however completely abolishing it[24]. NIV has also been shown to increase renin activity, both in animal and human models[25] and to increase sympathetic tone, for a secondary activation of the renin angiotensin aldosterone system. It results in a reduction in RBF, eGFR and diuresis[15]. Atrial natriuretic peptide suppression could also explain the lower urinary volume, and the reduction of urinary sodium excretion during NIV. Ramamoorthy et al[26] demonstrated, on canine models, how plasma ANP levels decreased with the onset of NIV. Some studies[27,28] have reported that mechanical ventilation can cause an inflammatory response, causing AKI. When ventilator support is mandatory, ventilatory settings seem to modify the occurrence of renal dysfunction. Ranieri's most recent prospective study[29] found a greater occurrence of renal failure in patients ventilated by conventional strategies, compared to those treated with protective strategies. Our study seems to confirm the association between impairment in hemodynamics and renal and endothelial dysfunction, during PEEP treatment, since NIV does not significantly impact on renal

function. In fact, there are no significant changes in RRI, AI and eGFR, suggesting a correct maintenance of renal flow, perhaps due to more conservative ventilation strategies. In addition, we also went to evaluate patients with chronic renal failure to better evaluate this effect. As we said, several mechanisms are implicated in renal dysfunction, but they are not completely understood. Mechanical ventilation could allow the release of systemic mediators of inflammation, which increase endothelial and epithelial permeability causing AKI[30-32]. Imai et al[27], in rabbit models, described the released of IL8 and induced renal and intestinal cell apoptosis due to invasive ventilation, providing evidence of a remote crosstalk triggered by lung damage. Mechanical ventilation appears to be an independent predictor for the development of renal failure in intensive care units. Vivino et al[33] assessed it in a studied on 153 traumatized patients which underwent invasive ventilation. Mechanical ventilation was indicated as an independent predictor of mortality and the need for dialysis replacement therapy by Chertow et al[34] studying 256 patients with acute tubular necrosis. In our study, we found an increase in the FMD value following the use of NIV. There are no similar evidences in literature, however, we can hypothesize that respiratory support could improve oxidative stress, increase the bioavailability of nitric oxide (NO), and then, improve the endothelial function. In fact, FMD is predominately mediated by the release of NO, a gaseous compound with antiadhesive, antithrombotic, and vasodilatory properties. This effect could reduce the cardiovascular risk of patients. Moreover, we showed a significant reduction of serum glucose, probably due to the better therapeutic control of patients after NIV. In fact, even a modest hyperglycaemia could reflect the physiological stress associated with impaired respiratory function. Chakrabarti et al[35] detected basal hyperglycemia as an independent prognostic negative value for the success of NIV therapy. NIV therapy, in accordance with its indications, has allowed an improvement of all ABG parameters. A correct acid-base balance, with a significant reduction in lactatemia, aid to preserve correct cardiac contractility. Lactic acid is produced by cellular metabolism, therefore, during hypoxic conditions cells can use less efficient energy production causing excessive production or poor elimination of lactates. In fact, high levels of lactates are also responsible for correct cardiac contractility, since acidosis, both respiratory and metabolic, is responsible for the deterioration of the cardiac inotropic state[36].

Limitation of the Study

The main limitation of our study is the small sample size; additional prospective follow-up studies, with a larger number of patients, are necessary to confirm our results. A significant proportion of patients were taking several medications with a potential bias on different metabolic indices.

Conclusions

The results of this study indicated that NIV has no significant negative effects on renal function in patients with respiratory failure, probably because positive pressure administered has not hemodynamic effect, causing low barotrauma, as reported in the literature. Furthermore, NIV has improved endothelial function in the short term, probably through the reduction of oxidative stress resulting by the improvement of the ABG parameters. NIV could help to reduce cardiovascular risk of patients also improving endothelial function and reducing serum glucose and lactatemia.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Consent to Publication

Informed consent was obtained from all individual participants included in the study.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article.

Funding

This study was not funded.

Authors' Contribution

SL, PP, SM designed the study; ADM, AM, DM, AM, AO, CMM recruited patients; AMP, AM, AM have performed clinical and instrumental tests; AM, SL, APM, FT analyzed and interpreted the patient data; SL was a major contributor in writing the manuscript. The manuscript has been seen and approved by all authors. The authors alone are responsible for the content and writing of the paper. The manuscript is not under consideration for publication elsewhere.

References

1) Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev 2009; 18: 213-221.
2) Criner GJ, Dreher M, Hart N, Murphy P. COPD home oxygen therapy and home mechanical ventilation: improving admission-free survival in persistent hypercapnic COPD. Chest 2018; 153: 1499-1500.
3) Wiles SP, Aboussouan LS, Mireles-Cabodevila E. Noninvasive positive pressure ventilation in stable patients with COPD. Curr Opin Pulm Med 2020; 26: 175-185.
4) Hess DR. The growing role of noninvasive ventilation in patients requiring prolonged mechanical ventilation. Respir Care 2012; 57: 900-918.
5) Chiumello D, Chevallard G, Gregoretti C. Non-invasive ventilation in postoperative patients: a systematic review. Intensive Care Med 2011; 37: 918-929
6) Li X, Hassoun HT, Santora R, Rabb H. Organ crosstalk: the role of the kidney. Curr Opin Crit Care 2009; 15: 481-487.
7) Pannu N, Mehta RL. Effect of mechanical ventilation on the kidney. Best Pract Res Clin Anaesthesiol 2004; 18: 189-203.
8) Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Int Med 2006, 145, 247-254.
9) Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, Vallance P, Vita J, Vogel R, International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002; 39: 257-265.
10) Ho CY, Solomon SD. A clinician's guide to tissue Doppler imaging. Circulation 2006; 113: 396-398.
11) Sawires H, Salah D, Hashem R, Ismail W, Salem A, Botros O, Seif H. Renal ultrasound and Doppler parameters as markers of renal function and histopathological damage in children with chronic kidney disease. Nephrology (Carlton) 2018; 23: 1116-1124.
12) Drury DR, Henry JP, Goodman J. The effects of continuous pressure breathing on kidney function. J Clin Invest 1947; 26: 945-9 51.
13) Gammanpila S, Bevan DR, Bhudu R. Effect of positive and negative expiratory pressure on renal function. Br J Anaesth 1977; 49: 199-205.
14) Marquez JM, Douglas ME, Downs JB, Wu WH, Mantini EL, Kuck EJ, Calderwood HW. Renal function and cardiovascular responses during positive airway pressure. Anesthesiology 1979; 50: 393-398.
15) Fewell JE, Bond GC. Renal denervation eliminates the renal response to continuous positive-pressure ventilation. Proc Soc Exp Biol Med 1979; 161: 574-578.
16) Hemmer M, Suter PM. Treatment of cardiac and renal effects of PEEP with dopamine in patients with acute respiratory failure. Anesthesiology 1979; 50: 399-403.
17) Järnberg PO, de Villota ED, Eklund J, Granberg PO. Effects of positive end-expiratory pressure on renal function. Acta Anaesthesiol Scand 1978; 22: 508-514.
18) Priebe HJ, Heimann JC, Hedley-Whyte J. Effects of renal and hepatic venous congestion on renal function in the presence of low and normal cardiac output in dogs. Circ Res 1980; 47: 883-890.
19) Mullins RJ, Dawe EJ, Lucas CE, Ledgerwood AM, Banks SM. Mechanisms of impaired renal function with PEEP. J Surg Res 1984; 37: 189-196.
20) Hall SV, Johnson EE, Hedley-Whyte J. Renal hemodynamics and function with continuous positive-pressure ventilation in dogs. Anesthesiology 1974; 41: 452-461.
21) Koyner JL, Murray PT. Mechanical ventilation and lung-kidney interactions. Clin J Am Soc Nephrol 2008; 3: 562-570.
22) Moore ES, Galvez MB, Paton JB, Fisher DE, Behrman RE. Effects of positive pressure ventilation on intrarenal blood flow in infant primates. Pediatr Res 1974; 8: 792-796.
23) Henry JP, Gauer OH, Reeves JL. Evidence of the atrial location of receptors influencing urine flow. Circ Res 1956; 4: 85-90.
24) Bark H, Le Roith D, Nyska M, Glick SM. Elevations in plasma ADH levels during PEEP ventilation in the dog: mechanisms involved. Am J Physiol 1980; 239: 474-481.
25) Annat G, Viale JP, Bui Xuan B, Hadj Aissa O, Benzoni D, Vincent M, Gharib C, Motin J. Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. Anesthesiology 1983; 58: 136-141.
26) Ramamoorthy C, Rooney MW, Dries DJ, Mathru M. Aggressive hydration during continuous positive-pressure ventilation restores atrial transmural pressure, plasma atrial natriuretic peptide concentrations, and renal function. Crit Care Med 1992; 20: 1014-1019.
27) 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.
28) Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory dis-

tress syndrome. N Engl J Med 2000; 342: 1301-1308.

29) Ranieri VM, Giunta F, Suter PM, Slutsky AS. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 2000; 284:43-44.

30) Floege J, Uhlig S. Kidney calling lung and call back: how organs talk to each other. Nephrol Dial Transplant 2010; 25: 32-34.

31) Slutsky AS, Tremblay LN. Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 1998; 157: 1721-1725.

32) Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342: 1301-1308.

33) Vivino G, Antonelli M, Moro ML, Cottini F, Conti G, Bufi M, Cannata F, Gasparetto A. Risk factors for acute renal failure in trauma patients. Intensive Care Med 1998; 24: 808-814.

34) Chertow GM, Lazarus JM, Paganini EP, Allgren RL, Lafayette RA, Sayegh MH. Predictors of mortality and the provision of dialysis in patients with acute tubular necrosis. The Auriculin Anaritide Acute Renal Failure Study Group. J Am Soc Nephrol 1998; 9: 692-698.

35) Chakrabarti B, Angus RM, Agarwal S, Lane S, Calverley PM. Hyperglycaemia as a predictor of outcome during non-invasive ventilation in decompensated COPD. Thorax 2009; 64: 857-862.

36) Mitchell JH, Wildenthal K, Johnson RL Jr. The effects of acid-base disturbances on cardiovascular and pulmonary function. Kidney Int 1972; 1: 375-389.