Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 79 (2016) 17–24

www.jcma-online.com

Original Article

Increased flow resistance and decreased flow rate in patients with acute respiratory distress syndrome: The role of autonomic nervous modulation

I-Chen Chen [a,b], Jane Kuo [c], Wen-Je Ko [b], Hsin-Chin Shih [a], Cheng-Deng Kuo [a,c,*]

[a] *Institute of Emergency and Critical Care Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*
[b] *Intensive Care Unit, National Taiwan University Hospital, Taipei, Taiwan, ROC*
[c] *Laboratory of Biophysics, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*

Received July 1, 2015; accepted July 19, 2015

Abstract

Background: The aim of this study was to investigate the flow resistance and flow rate in patients with acute respiratory distress syndrome (ARDS) in the surgical intensive care unit and their relation with autonomic nervous modulation.
Methods: Postoperative patients of lung or esophageal cancer surgery without ARDS were included as the control group ($n = 11$). Patients who developed ARDS after lung or esophageal cancer surgery were included as the ARDS group ($n = 21$). The ARDS patients were further divided into survivor and nonsurvivor subgroups according to their outcomes. All patients required intubation and mechanical ventilation.
Results: The flow rate was significantly decreased, while the flow resistance was significantly increased, in ARDS patients. The flow rate correlated significantly and negatively with positive end-expiratory pressure (PEEP), while the flow resistance correlated significantly and positively with PEEP in ARDS patients. Furthermore, the flow rate correlated significantly and negatively with the tidal volume-corrected normalized high-frequency power but correlated significantly and positively with the tidal volume-corrected low-/high-frequency power ratio. In contrast, the flow resistance correlated significantly and negatively with normalized very low-frequency power and tidal volume-corrected low-/high-frequency power ratio, but correlated significantly and positively with tidal volume-corrected normalized high-frequency power.
Conclusion: The flow rate is decreased and the flow resistance increased in patients with ARDS. PEEP is one of the causes of increased flow resistance and decreased flow rate in patients with ARDS. Another cause of decreased flow rate and increased flow resistance in ARDS patients is the increased vagal activity and decreased sympathetic activity. The monitoring of flow rate and flow resistance during mechanical ventilation might be useful for the proper management of ARDS patients.

Keywords: acute respiratory distress syndrome; autonomic; flow rate; flow resistance; intensive care unit; vagal

1. Introduction

Acute respiratory distress syndrome (ARDS)[1,2] is a life-threatening lung condition that affects patients with and without previous cardiopulmonary disorders. The signs and symptoms of ARDS usually begin within 72 hours of the initial insult or injury to the lung, and may include shortness of breath, fast breathing, and a low arterial oxygen tension. After lung resection or esophagectomy for esophageal cancer, ARDS may occur as a complication in some patients with an incidence of 1–3%.[3–6] ARDS is associated with a high mortality in patients who require mechanical ventilation and intensive care.[6] The overall mortality rate of ARDS is over 40%; it varies widely depending on disease severity and patient age.[5,7,8]

In patients with ARDS, mechanical ventilation with a lower tidal volume (V_T) than is traditionally used may result in

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Cheng-Deng Kuo, Laboratory of Biophysics, Department of Medical Research, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: cdkuo23@gmail.com (C.-D. Kuo).

http://dx.doi.org/10.1016/j.jcma.2015.10.001

decreased mortality,[9] and decelerating flow pattern associated with pressure modes is thought to provide better gas distribution than volume ventilation does.[10] Although mechanical ventilation provides essential life support, it can worsen lung injury. Mechanisms of ventilator-associated injuries include regional alveolar overdistention, repetitive alveolar collapse with shearing (atelectrauma), and oxygen toxicity.[11] To achieve a better outcome, pressure support or pressure control modes of ventilation is often adopted to minimize the incidence of barotrauma, including alveolar overdistention, pneumothorax, etc. Unfortunately, some important fluid mechanical parameters such as the flow rate and flow resistance of mechanical ventilation are not available in the ventilator settings when pressure control mode is used to ventilate ARDS patients.

Heart rate variability (HRV) analysis is a useful noninvasive method that can be used to evaluate the autonomic nervous modulation of patients with many kinds of illnesses. Several studies have documented the worse prognoses associated with autonomic dysfunction, including acute myocardial infarction,[12] septic shock,[13] and multiple organ failure.[14] Many factors have been found to interfere with the autonomic nervous modulation in critical care patients, such as ischemic heart disease,[15] sedative,[16] and vasoactive[17] drugs. In order to assess the autonomic nervous function of patients, baroreflex (BR) sensitivity may even be used in addition to HRV.

It is already known that respiratory activity and breathing pattern can affect the cardiac autonomic nervous modulation of a patient.[18] Thus, spectral analysis of heart rate, respiration, and blood pressure signals is a noninvasive approach that is widely used to investigate cardiovascular and cardiorespiratory control mechanisms.[19]

The first aim of this study was to obtain the flow rate and flow resistance of mechanically ventilated ARDS patients under pressure control mode, and to investigate the determinants of flow resistance and flow rate in patients with ARDS who required mechanical ventilation and critical care in the surgical intensive care unit (SICU) at a tertiary-care center. The second aim of this study was to investigate whether autonomic nervous modulation of mechanically ventilated ARDS patients played a role in the regulation of the flow rate and flow resistance.

2. Methods

2.1. Study design

This was a prospective cohort study with retrospective data analysis. The study protocol was approved by the Institute Review Board of the hospital, and written informed consent was obtained from the next-of-kin of the patients before their enrollment in the study.

2.2. Study setting and population

This study was conducted in the SICU of a tertiary medical center. All patients were older than 18 years and had received thoracic surgery due to lung or esophageal cancer. The patients were transferred to the SICU for postoperative care. Patients without postoperative complication of ARDS were enrolled as the control group. Patients complicated by ARDS were enrolled as the ARDS group. ARDS was diagnosed according to the Berlin Definition.[2] Three mutually exclusive categories of ARDS based on the degree of hypoxemia were proposed as the draft definition: mild [200 mmHg $<$ PaO_2/fraction of inspired oxygen (FIO_2) $\leq$ 300 mmHg], moderate (100 mmHg $<$ $PaO_2/FIO_2 \leq$ 200 mmHg), and severe ($PaO_2/FIO_2 \leq$ 100 mmHg) hypoxemia with four ancillary variables for severe ARDS: radiographic severity, respiratory system compliance ($\leq$ 40 mL/cmH_2O), positive end-expiratory pressure ($\geq$ 10 cmH_2O), and corrected expired volume per minute ($\geq$ 10 L/min). Patients who had severe coronary artery disease, persistent arrhythmia, cardiac pacing, diabetes mellitus, cerebral vascular accident, or major diseases of kidney or autoimmune system were excluded from the study.

2.3. Study protocol and data collection

All patients needed intubation and mechanical ventilation. Fentanyl was administered to all patients as an analgesic. The alveolar–arterial oxygen difference and Acute Physiology and Chronic Health Evaluation II score were determined for all ARDS patients when they were admitted to the SICU. The demographic data, vital signs, medications, ventilator readings, and relevant clinical data were recorded within 4 hours of admission to the SICU. Blood pressures were collected through the arterial line placed in the radial arteries of the patients and the bedside monitor of the SICU. Twelve minute electrocardiographic (ECG) signals were recorded in the supine position using the MP35 ECG device (BIOPAC Systems, Inc., Goleta, CA, USA). The output ECG signals were digitized by an A/D converter (BIOPAC Systems, Inc.), and stored in a notebook computer for later HRV analysis. During ECG recording, bedside care such as suction and invasive procedures that could interfere with HRV was avoided.

2.4. Flow rate and flow resistance

Flow rate is the amount of fluid flowing in a given length of time. It can be expressed as the volume of fluid stored during a given period of time. In fluid mechanics, the flow rate equals the volume of fluid divided by the time used to deliver the volume. Thus, the flow rate in mechanical ventilation is given by

$$F = \frac{V_T}{T_{insp}},$$

where F is the flow rate, V_T is the tidal volume, and T_{insp} is the inspiration time. The flow resistance is determined by the pressure applied onto the volume of fluid and the flow rate according to the well-known relationship among flow, pressure and resistance: $Q = \Delta P/R$. Thus, the flow resistance of air

during mechanical ventilation is given by the following equation:

$$R = \frac{P_{insp}}{F},$$

where R is the flow resistance and P_{insp} is the inspiratory pressure.

2.5. HRV analysis

The method used for HRV analysis has been described elsewhere and adheres to the standards laid down by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[19] In brief, the digitized ECG signals were retrieved to measure the consecutive RR intervals (RRI), which are the time intervals between successive pairs of QRS complexes, using the software developed for detection of the R-wave (Matlab 6.5, MathWorks Inc., Natick, MA, USA). All artifacts or ectopic beats were removed, and the resultant missing data were replaced by interpolated beats derived from the nearest valid data. If the percentage of deletion of artifacts or ectopic beats was more than 5% per record, then the patient was excluded from the study. The last 512 stationary RR intervals were obtained for power spectral HRV analysis.

The time domain HRV measures including mean RRI, standard deviation of RRI, coefficient of variation of RRI, and root mean squared successive difference of 512 RR intervals were calculated using standard formulae.

Power spectral analysis of the RR intervals was performed by means of fast Fourier transformation (Mathcad 11, Mathsoft Inc., Cambridge, MA, USA). The areas under the spectral peaks within the ranges of 0.01–0.04 Hz, 0.04–0.15 Hz, 0.15–0.4 Hz, and 0.01–0.4 Hz were defined as very low-frequency power (VLFP), low-frequency power (LFP), high frequency power (HFP), and total power (TP), respectively. The normalized VLFP (nVLFP = VLFP/TP × 100) was used as the index of renin–angiotensin–aldosterone modulation, thermal regulation, and vagal withdrawal; the normalized LFP (nLFP = LFP/TP × 100) was used as the index of combined sympathetic and vagal activities; the normalized HFP (nHFP = HFP/TP × 100) and HFP were used as the indices of cardiac vagal activity; and the low-/high-frequency power ratio (LHR = LFP/HFP) was used as the index of sympathovagal balance.[19] Since the pulmonary stretch receptors play a dynamic role in parasympathetic output, it was possible that the HFP and nHFP could be influenced by the V_T of the patients. Therefore, two parameters, HFP/V_T and $nHFP/V_T$, were used as the V_T-corrected indices of vagal activity in this study.[15]

2.6. Statistical analysis

The data are presented as mean ± standard deviation. Continuous variables were compared between the two groups of patients using Mann–Whitney U test (for non-normal distributed data) or independent samples *t*-test (for normally distributed data). The Chi-square test or Fisher's exact test, when appropriate, was used for comparisons of categorical data. Correlations among mechanical ventilation variables and arterial blood gas data were performed by using Pearson product moment correlation analysis and linear regression analysis. All statistical analyses were performed using a common statistical package (SigmaPlot13 for Windows, Systat Software, Inc., San Jose, CA, USA). A $p < 0.05$ was considered statistically significant.

3. Results

Eleven patients without ARDS and 21 patients with ARDS were included in this study. Midazolam (1–2 mg/h) was used to produce a state of calm or sleep in some patients in both groups of patients, and vasopressors (0.05–0.11 μg/kg/min) were used in eight patients in the ARDS group to maintain adequate blood pressure. Fentanyl (5–10 μg/h) was administered to all patients for pain control and the reduction of O_2 consumption in the ARDS group. The ECG recordings were taken within 4 hours of transfer to the SICU in all patients.

Table 1 compares the clinical characteristics, arterial blood gas data, and ventilator variables between the control patients and ARDS patients. There were no significant differences in the demographic data between the two groups. The ARDS patients had significantly higher systolic blood pressure and respiratory rates than the control patients, and more patients used midazolam and norepinephrine. Arterial blood gas analysis showed that the ARDS patients had significantly lower PaO_2 and PaO_2/FIO_2 but significantly higher $PaCO_2$ than control patients. Regarding ventilator settings, though the inspiratory pressure (P_{insp}) and inspiratory time were not significantly different between groups, the ARDS patients had significantly lower V_T and used significantly higher positive end-expiratory pressure (PEEP) and higher FIO_2 than the non-ARDS patients. The flow rate was significantly decreased, while the flow resistance was significantly increased, in the ARDS patients.

Table 2 compares the clinical characteristics, arterial blood gas data, and ventilator variables between the survivors and nonsurvivors among ARDS patients. The nonsurvivors had significantly higher $PaCO_2$ and P_{insp} than the survivors of ARDS.

Fig. 1 shows that the $PaCO_2$ correlated significantly and positively with the P_{insp} in the ARDS patients only. This result indicated that a higher inspiratory pressure was associated with an increased $PaCO_2$ in ARDS patients, but not in non-ARDS patients. The flow rate correlated significantly and negatively with the flow resistance in both groups of patients, demonstrating that increased flow resistance was associated with reduced flow rate in the mechanically ventilated patients regardless of their clinical illness. Fig. 1 also shows that the flow rate correlated significantly and negatively with PEEP while the flow resistance correlates significantly and positively with PEEP in the ARDS group only. This result indicated that

Table 1
Demographic and clinical data of the patients.

	Control[a] (n = 11)	ARDS[a] (n = 21)	p
Demographic			
Age (y)	61.4 ± 8.4	59.6 ± 16.5	NS
Sex, n (M/F)	5/6	17/4	NS
Body height (cm)	158.4 ± 10.3	164.7 ± 6.9	NS
Body weight (kg)	65.6 ± 9.4	65.1 ± 8.5	NS
Body temperature (°C)	36.4 ± 0.8	36.6 ± 0.7	NS
Vital signs			
SBP (mmHg)	115 ± 17	131 ± 23	0.041
DBP (mmHg)	63 ± 10	66 ± 13	NS
CVP (cm/H_2O)	10 ± 3	12 ± 3	NS
Respiratory rate (bpm)	13 ± 2	20 ± 6	0.001
Medications			
Midazolam (yes/no)	4/7	20/1	0.001
Norepinephrine (yes/no)	0/11	8/13	0.021
Arterial gas analysis			
PaO_2 (mmHg)	178.2 5 ± 4.4	82.8 ± 23.0	0.001
$PaCO_2$ (mmHg)	32.4 ± 5.8	37.9 ± 7.4	0.043
PaO_2/FIO_2 (mmHg)	444.5 ± 125.1	122.7 ± 49.7	0.001
Ventilator setting			
P_{insp} (cmH_2O)	20 ± 2	19 ± 3	NS
T_{insp} (sec)	0.9 ± 0.1	0.9 ± 0.1	NS
V_T (mL)	539 ± 94	427 ± 117	0.004
PEEP (cmH_2O)	5.8 ± 1.8	10.4 ± 3.0	0.001
MV (L/min)	7.1 ± 2.0	8.6 ± 3.2	NS
FIO_2	0.4 ± 0.1	0.7 ± 0.2	0.001
Derived data			
F (mL/sec)	574.8 ± 92.5	464.7 ± 116.2	0.012
R (cmH_2O·sec/mL)	0.03 ± 0.01	0.04 ± 0.01	0.009

ARDS = acute respiratory distress syndrome; bpm = beats per minute; CVP = central venous pressure; DBP = diastolic blood pressure; FIO_2 = fraction of inspired oxygen; F = flow rate; MV = minute ventilation; NS = not significant; $PaCO_2$ = partial pressure of arterial carbon dioxide; PaO_2 = partial pressure of arterial oxygen; PEEP = positive end-expiratory pressure; P_{insp} = inspiratory pressure; R = flow resistance; SBP = systolic blood pressure; T_{insp} = inspiration time; V_T = tidal volume.
[a] Data are presented as mean ± standard deviation.

Table 2
Demographic and clinical data of survivors and nonsurvivors of acute respiratory distress syndrome.

	Survivor[a] (n = 16)	Nonsurvivor[a] (n = 5)	p
Demographic			
Age (y)	56.6 ± 17.0	69.0 ± 11.6	NS
Sex, n (M/F)	14/2	3/2	NS
Body height (cm)	165.3 ± 6.6	164.7 ± 6.9	NS
Body weight (kg)	164.7 ± 6.9	67.2 ± 11.6	NS
Body temperature (°C)	36.6 ± 0.7	36.4 ± 0.6	NS
Vital signs			
SBP (mmHg)	132.4 ± 23.1	125.4 ± 26.5	NS
DBP (mmHg)	67.6 ± 11.4	60.4 ± 16.9	NS
CVP (cmH_2O)	11.1 ± 2.7	13.0 ± 5.0	NS
RR (bpm)	19.1 ± 6.1	24.2 ± 4.8	NS
Medications			
Midazolam (yes/no)	15/1	5/0	NS
Norepinephrine (yes/no)	6/10	2/3	NS
Arterial gas analysis			
PaO_2 (mmHg)	82.0 ± 24.6	85.3 ± 18.9	NS
$PaCO_2$ (mmHg)	36.0 ± 6.0	44.2 ± 8.6	0.043
PaO_2/FIO_2	122.8 ± 52.1	122.7 ± 46.5	NS
Score			
ALI score	13 ± 2	13 ± 2	NS
$AaDO_2$ (mmHg)	474.2 ± 134.8	472.4 ± 121.7	NS
APACHE II	15 ± 6	15 ± 6	NS
Ventilator setting			
P_{insp} (cmH_2O)	18.4 ± 3.4	21.4 ± 1.3	0.039
T_{insp} (sec)	0.9 ± 0.1	0.9 ± 0.1	NS
V_T (mL)	436.3 ± 119.5	397.2 ± 117.9	NS
PEEP (cmH_2O)	10.1 ± 3.2	11.3 ± 2.3	NS
MV (L/min)	8.2 ± 2.8	10.0 ± 3.7	NS
FIO_2	0.7 ± 0.2	0.9 ± 0.1	NS
Flow data			
F (mL/sec)	470.3 ± 118.2	446.9 ± 120.3	NS
R (cmH_2O·sec/mL)	0.04 ± 0.01	0.05 ± 0.02	NS

$AaDO_2$ = alveolo–arterial oxygen difference; ALI score = acute lung injury score; APACHE II = Acute Physiology and Chronic Health Evaluation II; ARDS = acute respiratory distress syndrome; BP = systolic blood pressure; bpm = beats per minute; CVP = central venous pressure; DBP = diastolic blood pressure; F = flow rate; FIO_2 = fraction of inspired oxygen; MV = minute ventilation; NS = not significant; $PaCO_2$ = partial pressure of arterial carbon dioxide tension; PaO_2 = partial pressure of arterial oxygen tension; PEEP = positive end-expiratory pressure; P_{insp} = inspiratory pressure; R = flow resistance; RR = respiratory rate; SBP = systolic blood pressure; T_{insp} = inspiration time; V_T = tidal volume.
[a] Data are presented as mean ± standard deviation.

the use of higher PEEP in ARDS patients was the cause of decreased flow rate and increased flow resistance.

Fig. 2 further shows that in the ARDS patients, the flow rate correlated significantly and negatively with the tidal volume-corrected normalized high-frequency power ($nHFP/V_T$) but correlated significantly and positively with the $LHR*V_T$. In contrast, the flow resistance correlated significantly and negatively with nVLFP and $LHR*V_T$, but correlated significantly and positively with $nHFP/V_T$. These results suggest that enhanced vagal activity and suppressed sympathetic activity were associated with an increased flow resistance and decreased flow rate in the ARDS patients.

4. Discussion

This study investigated the flow resistance and flow rate in mechanically ventilated ARDS patients in the SICU, and their relation with autonomic nervous modulation. Our results showed that the resistance to airflow was increased and the flow rate was decreased in ARDS patients in comparison with non-ARDS patients. The use of higher PEEP might be the cause of increased flow resistance and decreased flow rate in ARDS patients. The nonsurvivor ARDS patients were found to have higher $PaCO_2$ than the survivor ARDS patients, despites the use of higher inspiratory pressure. Further analysis showed that increased vagal activity and decreased sympathetic activity might be the cause of increased flow resistance and decreased flow rate in ARDS patients.

Pressure control mode of ventilation is often used in mechanically ventilated ARDS patients to minimize the incidence of barotrauma and obtain a better outcome. The decelerating flow pattern associated with pressure modes is thought to provide better gas distribution than volume ventilation.[10] Unfortunately, fluid mechanical parameters such as flow rate and flow resistance cannot be obtained and used for

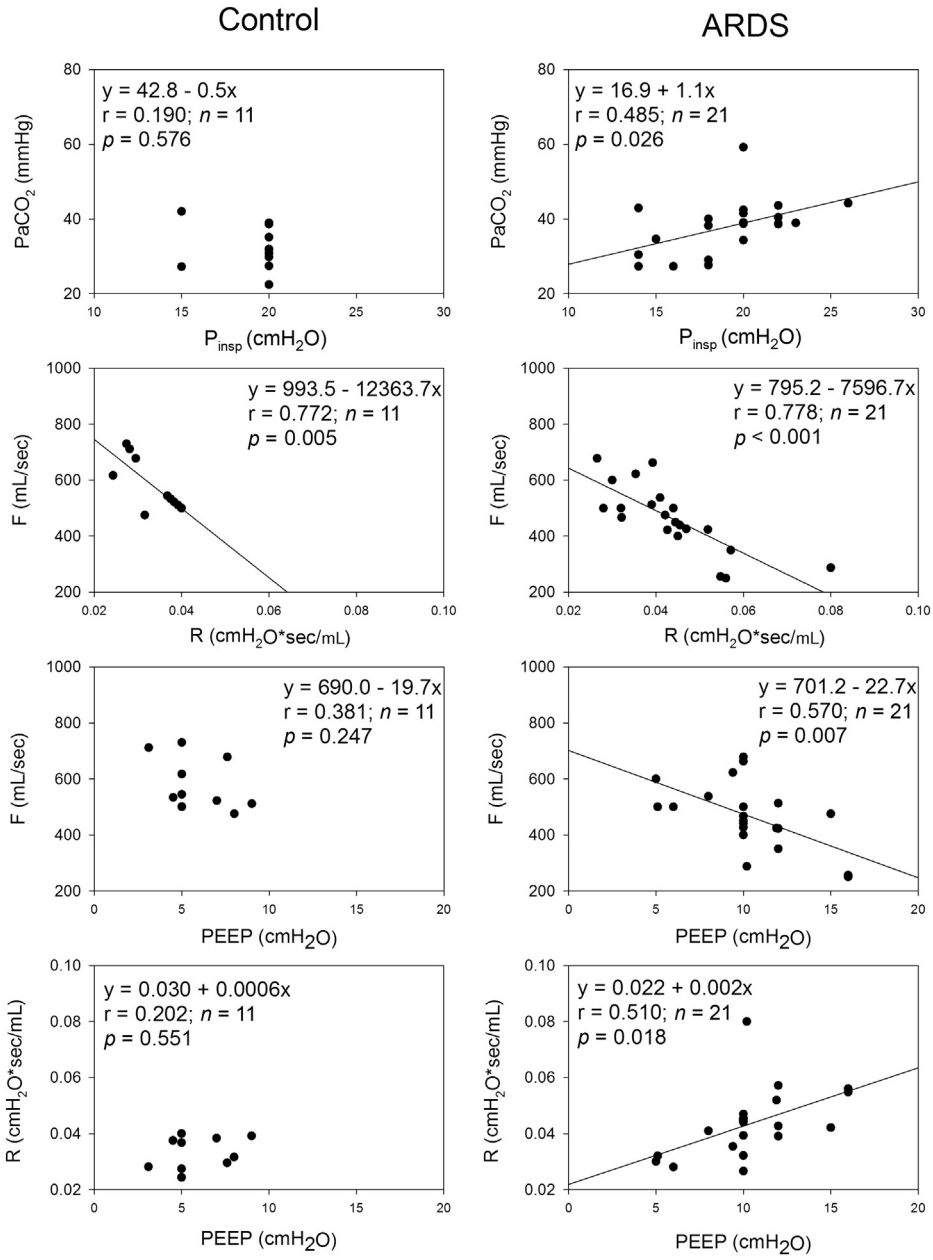

Fig. 1. The correlations among various variables of mechanical ventilation in the control and acute respiratory distress syndrome groups. ARDS = acute respiratory distress syndrome; F = flow rate; $PaCO_2$ = arterial carbon dioxide tension; PEEP = positive end-expiratory pressure; P_{insp} = inspiratory pressure; R = resistance.

bedside monitoring of the patients when the pressure control mode of ventilation is used. To overcome this limitation, we used two simple equations to obtain the flow rate and flow resistance of mechanical ventilation, and compared them between ARDS and non-ARDS patients. We found that these two parameters were indeed different between ARDS and non-ARDS patients. The ARDS patients had decreased flow rate and increased flow resistance, as compared with the non-ARDS patients. The high level of PEEP was found to be one of the causes of decreased flow rate and increased flow resistance in ARDS patients during mechanical ventilation with linear regression analysis. Another factor leading to decreased flow rate and increased flow resistance was found to be increased vagal activity and decreased sympathetic activity in the ARDS patients. There might be other causes in addition to high PEEP and autonomic dysfunction. For instance, stiff lung due to consolidation of lung parenchyma might be one of the factors resulting in decreased flow rate and increased flow resistance in ARDS. These factors should be corrected before the lung condition can be improved in ARDS patients.

In our study, the use of high PEEP might be one the causes of the increase in $PaCO_2$ and flow resistance and the decrease in flow rate in ARDS patients. However, the use of PEEP is inevitable because of severe hypoxemia in ARDS patients.

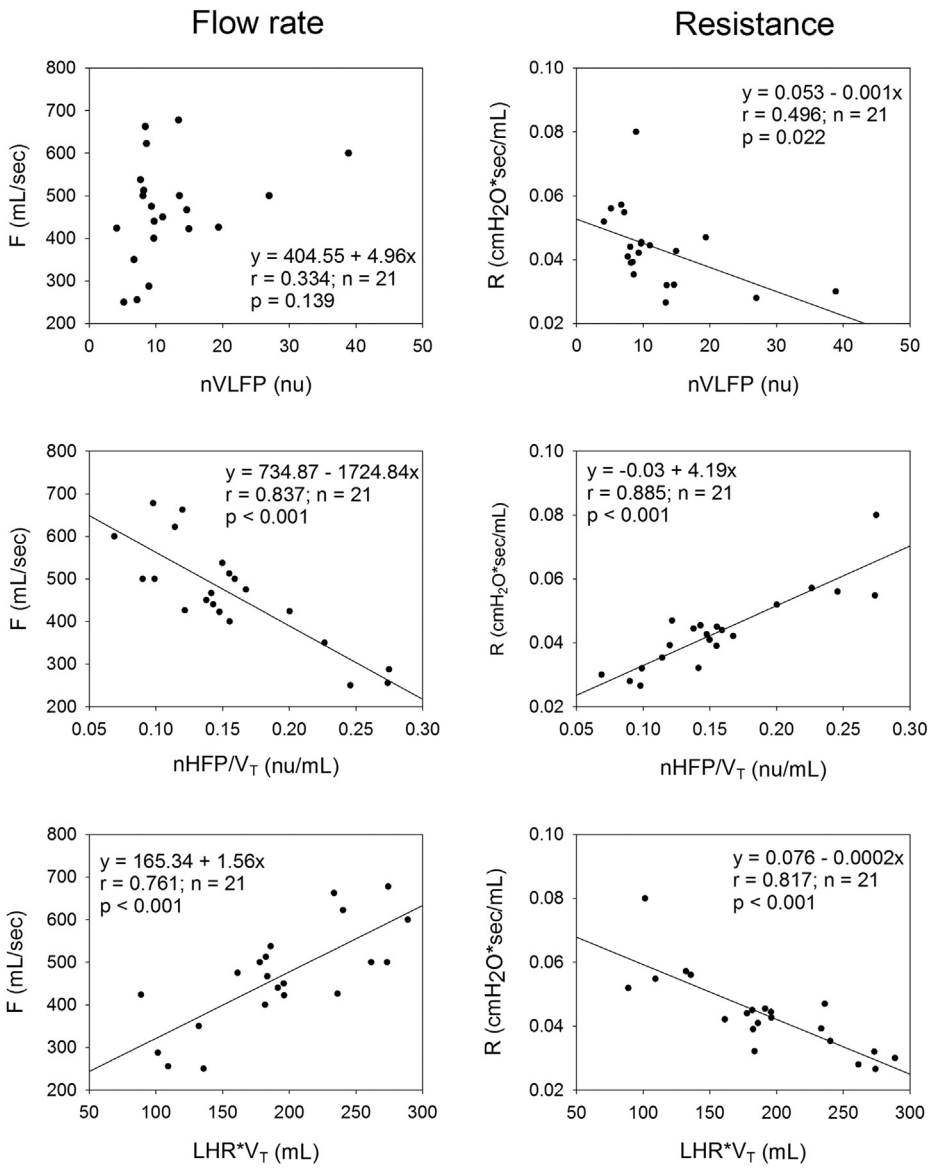

Fig. 2. The correlations between flow rate and resistance and heart rate variability measures in the acute respiratory distress syndrome patients. ARDS = acute respiratory distress syndrome; F = flow rate; LHR = low-/high-power ratio; nHFP = normalized high-frequency power; nVLFP = normalized very low-frequency power; R = resistance; V_T = tidal volume.

The goal of applying PEEP to an ARDS lung is to recruit those lung units that are both nonaerated and reopenable and to keep them open. Furthermore, lung overdistension should be avoided or prevented as much as possible.[20] The basic physiological effect of PEEP is to induce an increase in functional residual capacity and lung volumes, alveolar recruitment, redistribution of extravascular lung water, and improved ventilation-perfusion matching.[20,21] Increasing PEEP is recommended in the treatment of hypoxemia and is routinely prescribed in the SICU for ARDS patients. Furthermore, PEEP in patients with ARDS was associated with a reduction in cardiac output, and changes in cardiac output were significantly and positively correlated with the changes in the intrapulmonary shunt.[22] Higher PEEP can increase right ventricle afterload and impair right ventricle function. It may also contribute to acute cor pulmonale in ARDS, in whom the reported incidence is almost 25%.[23] Systemic vascular resistance was unchanged, but pulmonary vascular resistance doubled upon addition of PEEP.[21] Pulmonary blood flow is compromised to lung regions that remain well ventilated. The expected consequence of increased PEEP level would be an increase in the physiological dead space, and the increase in dead space represents an impaired ability to excrete carbon dioxide.[24]

It is already known that respiratory rate and V_T can modify the HRV during a period of constant CO_2 concentration.[25] The respiratory modulation of HRV is known to be frequency-dependent, and the impact of respiration on HRV is exacerbated when the respiration rate falls within the low-frequency (LF) band.[26] During mechanical ventilation, stable high-

frequency (HF)-RR amplitude and cardiorespiratory phase difference over time reflect a blunted autonomic nervous function which might worsen as PEEP increases.[27] Breathing to a metronome has been reported to increase heart rate spectral power in the HF or respiratory frequency region. Some studies have shown that in healthy awake normal individuals, exposure to a modest level of PEEP results in significant changes in hemodynamics and in neural circulatory control (increase in blood pressure, decrease in HR and increase in the HF components of the BR), compared with controlled breathing.[28,29] Guilleminault et al[30] indicated that the HF component was only significantly decreased in patients with upper airway resistance syndrome, which indicates a predominant involvement of the vagal tone in patients with upper airway resistance syndrome in comparison to those with obstructive sleep apnea syndrome. Poyhonen et al[31] showed that adding CO_2 to the inspiratory gas increased HF and LF components of HRV in awake volunteers during both spontaneous and mechanical ventilation, and that $PaCO_2$, V_T and respiratory rate should be controlled when HRV power spectrum was measured in conscious patients or volunteers. Change of HRV between different ventilator settings has also been described in a canine model. These data indicated that there was a relative shift in autonomic balance to increased sympathetic and decreased parasympathetic tone with exposure to mechanical ventilation. The increase in intrathoracic pressure might reduce the right ventricular end-diastolic volume (preload). These hemodynamic alterations might generate a change in autonomic tone, so that the cardiac output could be maintained.[32] These findings may contribute to understanding the mechanisms, indications, and effectiveness of positive pressure breathing strategies in treating cardiorespiratory and other disease conditions.[28] The selective increase in the HF and not in the LF a-index of BR sensitivity supports a potential important role of enhanced vagal activity, which is also suggested by the increase in the HF component of HRV. In agreement with the abovementioned studies, our results indicated that increased vagal activity ($nHFP/V_T$) and decreased sympathetic activity (nVLFP) might be associated with an increase in flow resistance and decrease in flow rate in ARDS patients.

The flow rate and flow resistance defined and obtained in this study are expected to be useful in the clinical monitoring and management of not only ARDS patients but also other kinds of patients so long as they are mechanically ventilated using pressure control or pressure support mode. These two fluid mechanical parameters can also be used to monitor patients in a real-time fashion to achieve a better mechanical support of patients without additional device or equipment. It is therefore suggested that the values of these two parameters be displayed in the display panel of the ventilator so that the respiratory therapists and intensivists can have a better understanding about the progression of the lung diseases of the patients at any time.

In conclusion, the flow rate and flow resistance during mechanical ventilation were defined and compared between ARDS and non-ARDS patients. The flow resistance was increased while the flow rate was decreased in ARDS patients compared with non-ARDS patients. The use of high PEEP was one of the causes of increased flow resistance and decreased flow rate in ARDS patients. Another cause of decreased flow rate and increased flow resistance in ARDS patients was the increase in vagal activity and the decrease in sympathetic activity. The monitoring of flow rate and flow resistance during mechanical ventilation might be useful for the proper management of ARDS patients in the SICU.

Acknowledgments

This study was supported by in part by a grant VGHUST97-P1-03 from the Veterans General Hospitals University System of Taiwan Joint Research Program, Taiwan, and the grants 96VN-010 and VN99-14 from the Taipei Veterans General Hospital-National Taiwan University Hospital Joint Research Program, Taipei, Taiwan.

References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;**2**:319−23.
2. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;**307**:2526−33.
3. D'Journo XB, Michelet P, Avaro JP, Trousse D, Giudicelli R, Fuentes P, et al. Respiratory complications after oesophagectomy for cancer. *Rev Mal Respir* 2008;**25**:683−94.
4. Kim JB, Lee SW, Park SI, Kim YH, Kim DK. Risk factor analysis for postoperative acute respiratory distress syndrome and early mortality after pneumonectomy: the predictive value of preoperative lung perfusion distribution. *J Thorac Cardiovasc Surg* 2010;**140**:26−31.
5. Kometani T, Okamoto T, Yoshida S, Yoshino I. Acute respiratory distress syndrome after pulmonary resection. *Gen Thorac Cardiovasc Surg* 2013;**61**:504−12.
6. Dulu A, Pastores SM, Park B, Riedel E, Rusch V, Halpern NA. Prevalence and mortality of acute lung injury and ARDS after lung resection. *Chest* 2006;**130**:73−8.
7. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000;**342**:1334−49.
8. Tandon S, Batchelor A, Bullock R, Gascoigne A, Griffin M, Hayes N, et al. Peri-operative risk factors for acute lung injury after elective oesophagectomy. *Br J Anaesth* 2001;**86**:633−8.
9. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;**342**:1301−8.
10. Davis Jr K, Branson RD, Campbell RS, Porembka DT. Comparison of volume control and pressure control ventilation: is flow waveform the difference? *J Trauma* 1996;**41**:808−14.
11. Slutsky AS. Lung injury caused by mechanical ventilation. *Chest* 1999;**116**:S9−15.
12. Liu PY, Tsai WC, Lin LJ, Li YH, Chao TH, Tsai LM, et al. Time domain heart rate variability as a predictor of long-term prognosis after acute myocardial infarction. *J Formos Med Assoc* 2003;**102**:474−9.
13. Chen WL, Kuo CD. Characteristics of heart rate variability can predict impending septic shock in emergency department patients with sepsis. *Acad Emerg Med* 2007;**14**:392−7.
14. Pontet J, Contreras P, Curbelo A, Medina J, Noveri S, Bentancourt S, et al. Heart rate variability as early marker of multiple organ dysfunction syndrome in septic patients. *J Crit Care* 2003;**18**:156−63.

15. Chen WL, Tsai TH, Huang CC, Chen JH, Kuo CD. Heart rate variability predicts short-term outcome for successfully resuscitated patients with out-of-hospital cardiac arrest. *Resuscitation* 2009;**80**:1114−8.
16. Win NN, Fukayama H, Kohase H, Umino M. The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. *Anesth Analg* 2005;**101**:97−102.
17. Kasaoka S, Nakahara T, Kawamura Y, Tsuruta R, Maekawa T. Real-time monitoring of heart rate variability in critically ill patients. *J Crit Care* 2010;**25**:313−6.
18. Koizumi K, Terui N, Kollai M. Neural control of the heart: significance of double innervation re-examined. *J Auton Nerv Syst* 1983;**7**:279−94.
19. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996;**93**:1043−65.
20. Guerin C. The preventive role of higher PEEP in treating severely hypoxemic ARDS. *Minerva Anestesiol* 2011;**77**:835−45.
21. Qvist J, Pontoppidan H, Wilson RS, Lowenstein E, Laver MB. Hemodynamic responses to mechanical ventilation with PEEP: the effect of hypervolemia. *Anesthesiology* 1975;**42**:45−55.
22. Dantzker DR, Lynch JP, Weg JG. Depression of cardiac output is a mechanism of shunt reduction in the therapy of acute respiratory failure. *Chest* 1980;**77**:636−42.
23. Vieillard-Baron A, Schmitt JM, Augarde R, Fellahi JL, Prin S, Page B, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. *Crit Care Med* 2001;**29**:1551−5.
24. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002;**346**:1281−6.
25. Brown TE, Beightol LA, Koh J, Eckberg DL. Important influence of respiration on human R-R interval power spectra is largely ignored. *J Appl Physiol* 1993;**75**:2310−7.
26. Beda A, Jandre FC, Phillips DI, Giannella-Neto A, Simpson DM. Heart-rate and blood-pressure variability during psychophysiological tasks involving speech: influence of respiration. *Psychophysiology* 2007;**44**:767−78.
27. Van de Louw A, Medigue C, Papelier Y, Cottin F. Positive end-expiratory pressure may alter breathing cardiovascular variability and baroreflex gain in mechanically ventilated patients. *Respir Res* 2010;**11**:38−49.
28. Fietze I, Romberg D, Glos M, Endres S, Theres H, Witt C, et al. Effects of positive-pressure ventilation on the spontaneous baroreflex in healthy subjects. *J Appl Physiol* 2004;**96**:1155−60.
29. Torok T, Rudas L, Kardos A, Paprika D. The effects of patterned breathing and continuous positive airway pressure on cardiovascular regulation in healthy volunteers. *Acta Physiol Hung* 1997;**85**:1−10.
30. Guilleminault C, Poyares D, Rosa A, Huang YS. Heart rate variability, sympathetic and vagal balance and EEG arousals in upper airway resistance and mild obstructive sleep apnea syndromes. *Sleep Med* 2005;**6**:451−7.
31. Poyhonen M, Syvaoja S, Hartikainen J, Ruokonen E, Takala J. The effect of carbon dioxide, respiratory rate and tidal volume on human heart rate variability. *Acta Anaesthesiol Scand* 2004;**48**:93−101.
32. Frazier SK, Moser DK, Stone KS. Heart rate variability and hemodynamic alterations in canines with normal cardiac function during exposure to pressure support, continuous positive airway pressure, and a combination of pressure support and continuous positive airway pressure. *Biol Res Nurs* 2001;**2**:167−74.