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Spontaneous variability of arterial oxygenation in critically ill mechanically ventilated patients

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Abstract *Objective*: To assess the magnitude of spontaneous variability of arterial oxygenation and oxygen tension-based indices over time in medical intensive care unit (ICU) patients and to study whether high positive end-expiratory pressure (PEEP) or inverse inspiratory-to-expiratory (I:E) ratio ventilation (IRV) results in a greater variability than low PEEP with conventiona l I:E ratio ventilation.
Design: Prospective study.
Setting: Medical ICU in a tertiary medical center.
Participants: 23 patients requiring a pulmonary artery floating catheter for hemodynamic monitoring.
Intervention: After being completely sedated, patients were randomized to receive pressure-control ventilation at setting A: high PEEP (15 cmH_2O) with conventional I:E ratio (1:2) and setting B: inverse I:E ratio (2:1) with low PEEP (5 cmH_2O) alternately, and then at setting C: low PEEP (5 cmH_2O) with conventional I:E ratio (1:2). Each ventilation setting lasted 1 h.
Measurements and results: The arterial and mixed venous blood samples were measured simultaneously at baseline (time 0), and at 15, 30, 45, and 60 min thereafter. The coefficient of variation (CV) of arterial oxygen tension (PaO_2) over time was 5.9 % for setting A, 7.2 % for setting B, and 6.9 % for setting C. ANOVA showed no significant differences in CVs of PaO_2 between the three settings. Oxygen tension-based indices, alveolar-arterial oxygen difference ($A\text{-}aDO_2$) and PaO_2/PAO_2 (alveolar oxygen tension), displayed CV s equal to that of PaO_2; the CV of $A\text{-}aDO_2/PaO_2$ was significantly greater than that of PaO_2.
Conclusions: In critically ill medical ICU patients, despite sedation, the spontaneous variability in PaO_2 over time is substantial. A high PEEP or IRV does not contribute to the increased variation in PaO_2.

Key words Spontaneous variability · Mechanical ventilation · Arterial oxygenation · Positive end-expiratory pressure · Inverse ratio ventilation · Venous admixture

Introduction

The most important clinical applications for arterial blood gas (ABG) measurements include: (1) assessment of acid-base disorders, (2) detection and quantification of hypoxia and hyperoxia, (3) detection of hypercapnia and (4) calculations of cardiac output, dead space ventilation, and right-to-left shunts [1]. For patients with respiratory failure, serial ABGs are evaluated to monitor a patient's progress, to adjust oxygen and other medication regimens, and to make management decisions concerning assisted ventilation, positive end-expiratory

pressure (PEEP), and weaning from ventilatory support [2].

The factors affecting the accuracy and precision of blood gas analysis have been well studied, and sound guidelines for obtaining and handling blood gas samples have been established [3]. Nonetheless, only a few authors have discussed spontaneous variability in ABG over time in intensive care unit (ICU) patients with respiratory failure [4–6]. They found that the spontaneous variability of blood gases is substantial even in stable ICU patients and recommended that trends in arterial oxygen tension (PaO_2) over time may be a more reliable guide to decision making than isolated changes without appropriate clinical correlations. In these studies, however, patients remained free to move about and were exposed to the influences of a noisy external environment. We thought that the spontaneous variability would be more authentic if all extraneous and intrinsic interference was eliminated through sedation.

High level PEEP [7–9] and inverse inspiratory-to-expiratory ratio (I:E) ventilation (IRV) [9, 10] are two important settings for improving arterial oxygenation in severely hypoxemic patients or in the acute respiratory distress syndrome (ARDS). For these seriously ill patients, a small deterioration in ABG may be of critical importance, necessitating emergency intervention. Therefore, it is important to distinguish whether this change represents a significant worsening in the clinical condition or simply a spontaneous individual patient variation. However, it is not currently known whether the more complex mechanical ventilatory settings (high PEEP or IRV), which we use to recruit the collapsed alveoli and reduce the ventilation-perfusion mismatch, contribute to a greater degree of spontaneous variation in arterial blood analysis in these critically ill patients.

Oxygen tension-based indices [alveolar-arterial oxygen difference ($A\text{-}aDO_2$), arterial/alveolar oxygen tension ratio (Pa/AO_2), PaO_2/FIO_2 (fractional inspired oxygen), and $A\text{-}aDO_2/PaO_2$] are often used as alternatives to determine the venous admixture (Q_s/Q_t) in order to assess the efficiency of pulmonary oxygenation when a pulmonary artery catheter is not in use [11–14]. The accuracy and reliability of these indices to reflect Q_s/Q_t have been investigated extensively [12, 15–17]; however, no study compared the stability of these indices over time with PaO_2 and Q_s/Q_t.

The aim of this study was to evaluate, with patients completely sedated, the magnitude of the spontaneous variability of PaO_2 over a brief period in medical ICU patients undergoing mechanical ventilation at the following settings: (A) high PEEP (15 cmH_2O) with conventional I:E ratio (1:2), (B) IRV (2:1) with low PEEP (5 cmH_2O), and (C) low PEEP (5 cmH_2O) with conventional I:E ratio (1:2), and whether patients ventilated with high PEEP (setting A) or IRV (setting B) will display a larger spontaneous variability in PaO_2 than patients ventilated with setting C. We also tried to clarify whether these tension-based indices of oxygenation have a different spontaneous variability from PaO_2.

Materials and methods

Patients

The study group consisted of 23 patients with acute respiratory failure (mean age 55 ± 20 years, range 19–85 years, 9 males, 14 females) from the medical ICU of Chang Gung Memorial Hospital. Because arterial oxygenation is affected by cardiac output (CO), al l patients selected had a pulmonary artery floating catheter (Intellicath, 7.5F, Baxter Edwards Critical-Care, Irvine, Calif., USA) inserted for hemodynamic monitoring. The position of the catheter was verified by a chest roentgenogram and by obtaining a pulmonary artery occlusion pressure tracing using 1.0 to 1.5 ml of air. Only patients who survived the initial critical stage, and whose hemodynamics were judged to be clinically stable, were enrolled, although vasoactive drugs with dopamine and/or dobutamine, and/or norepinephrine were still needed in 14 of the 23 (3/5) patients. The relevant clinical data are listed in Table 1. The Acute Physiology and Chronic Health Evaluation III score [18] and acute lung injury score [19] at the time of the study ranged from 26 to 120 (mean 67 ± 24) and 1 to 3.3 (mean 2.1 ± 0.6), respectively. An arterial catheter was inserted for hemodynamic monitoring and blood gas sampling in each patient. Each patient completed the study uneventfully. The study was approved by the Institutional Review Board for Human Research of C hang Gung Memorial Hospital. Informed written consent was obtained from the nearest relative after a full explanation of the nature of the study.

Mechanical ventilation settings

The patients were ventilated with the intensive care ventilator Servo 300 (Siemens-Elema, Lund, Sweden) or PB-7200 (Puritan-Bennett Int'l, Carlsbad, Calif., USA). The ventilatory mode was pressure-control mode. Each patient underwent all three ventilatory settings: (A) high PEEP (15 cmH_2O) with conventional I:E ratio (1:2) ventilation, (B) inverse I:E ratio (2:1) ventilation with low PEEP (5 cmH_2O), and (C) low PEEP (5 cmH_2O) with conventional I:E ratio (1:2) ventilation. The values for FIO_2 ranged from 30 to 60%. The respiratory rates and tidal volumes were set at 20 breaths/min and 8–10 ml/kg, respectively. The tidal volumes during the three setting periods were kept similar by adjusting the levels of inspiratory pressure.

Hemodynamic monitoring and recording of CO

Hemodynamics, including systolic, mean systemic, and pulmonary arterial pressures, as well as heart rates during the time of blood gas sampling were recorded from an on-line HP Component Monitoring System (Hewlett-Packard Model 56 S, M 1165 A, Boblingen, Germany). The CO computer (Vigilance Monitor, Baxter Edwards Critical Care) used in this study, along with the pulmonary artery catheter (IntelliCath), can monitor CO automatically and continuously using thermodilution principles and stochastic system identification techniques [20]. Its accuracy and precision have been evaluated by Yelderman et al. in animals [21] and in human pa-

Table 1 Patient's clinical characteristics (*APACHE III* Acute Physiology, Age, Chronic Health Evaluation III, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *SLE* systemic lupus erythematosus, *DM* diabetes mellitus, *CHF* congestive heart failure, *CMV* cytomegalovirus, *TB* tuberculosis, *AMI* acute myocardial infarction, *DIC* disseminated intravascular coagulation)

Case	Age (years)	Sex	APACHE III score	ALI score	Outcome	Diagnosis
1	64	M	92	3	Alive	ARDS, pneumonia, non-Hodgkin lymphoma
2	26	F	72	2	Alive	Pulmonary hemorrhage, SLE, acute renal failure
3	85	M	54	3.25	Died	ARDS, pneumonia
4	19	F	105	2	Died	ARDS, sepsis, SLE, acute renal failure
5	75	M	83	2	Died	Acute pulmonary edema, heart failure
6	73	F	120	1	Died	Septic shock, DM, cervical carcinoma
7	57	F	40	2.25	Alive	ARDS, pneumonia
8	19	F	29	2.75	Alive	ARDS, SLE
9	85	M	61	2.5	Alive	ARDS
10	42	F	73	1.75	Died	SLE, pulmonary hemorrhage
11	35	F	62	2.5	Alive	Pulmonary hemorrhage, SLE, acute renal failure
12	73	F	49	3	Alive	Acute pulmonary edema, DM
13	43	M	69	2.5	Alive	ARDS, pneumonia, liver cirrhosis
14	79	F	98	2	Died	Sepsis, CHF, DM
15	65	F	50	1.75	Alive	Sepsis, DM, acute renal failure
16	48	F	53	2	Died	Sepsis, SLE, acute renal failure
17	38	F	26	2.25	Alive	CMV pneumonitis, SLE
18	64	F	84	2.25	Alive	Sepsis, acute pulmonary edema, DM
19	58	M	55	1.25	Alive	Septic shock, pneumonia
20	66	M	66	1.5	Died	Septic shock, pulmonary TB
21	58	M	66	1.75	Died	Acute pulmonary edema, AMI
22	54	M	38	2.25	Alive	ARDS, pneumonia, DM, alcoholism
23	29	F	93	1.5	Alive	ARDS, DIC

tients [22] with good results. The displayed values at the time of blood sampling were recorded to represent the CO related to that PaO_2 analysis.

Blood gas analysis

Arterial blood and mixed venous blood gas samples were obtained simultaneously from the arterial cannula and pulmonary artery catheter. When blood samples were being aspirated, the catheter line was cleared of contamination from the anticoagulant saline solution before collection. About 3–4 ml of solution and blood was aspirated into a secondary "waste" syringe until only fresh arterial blood filled the sampling catheter, and about 2 ml of arterial blood was drawn into a heparinized plastic syringe. The liquid heparin was completely expelled fro m the syringe to prevent heparin dilution before drawing. All air bubbles were immediately removed from the sample after drawing, and the syringe was sealed with a neoprene cap to prevent contamination with air. The blood gas samples were kept anaerobically and analyzed as soon as possible for PaO_2, arterial carbondioxide tension, pH, arterial O_2 saturation (SaO_2), and bicarbonate with a blood gas analyzer (Corning 178, Ciba Corning Diagnostic, Mass., USA) at room temperature in our ICU. Q_s/Q_t was calculated as $Q_s/Q_t = (Cc'O_2\text{-}CaO_2) / (Cc'O_2\text{-}CvO_2)$, where CaO_2 and CvO_2 represented the O_2 content of the systemic artery and mixed venous blood, respectively. They were calculated as {[hemoglobin (g/100 ml) x 1.36 x (SaO_2 or SvO_2)] + 0.003 x (PaO_2 or PvO_2)}. $Cc'O_2$ represented the O_2 content of end-capillary blood and was derived from the same equation. The PcO_2, capillary O_2 partial pressure, was assumed to be equal to the alveolar O_2 partial pressure (PAO_2).

The corning 178 analyzer automatically performed a one-point calibration every 30 min and a two-point calibration every 2 h. Regularly scheduled maintenance was performed in accordance with the manufacturer's recommendations to ensure reliable operation of the analyzer.

Study protocol

Patients were completely sedated with a continuous intravenous infusion of midazolam or propofol 2–3 h before the study to prevent them fighting with the ventilator and to minimize external or intrinsic interference with the patient's arterial oxygenation. The levels of sedation were all deeper t han level 4–5 of the Ramsey sedation score [23]. Patients were randomized to receive setting A and setting B alternately, and then finally setting C. Each setting period lasted 1 h. The baseline blood sample was drawn at least 1 h after the adjustment of each ventilator setting to allow for equilibration, following which, four additional samples were obtained sequentially at 15-min intervals. During the three study periods, the rate of intravenous fluid and vasopressor infusion was kept fixed. No nasogastric feeding, medication changes, or other therapeutic interventions were permitted. Endotracheal suctioning was performed only at the equilibration periods and was withheld during the recording of arterial oxygenation. FIO_2 and ventilator settings were also held constant.

Statistical analysis

The results obtained are expressed as means ± standard deviation (SD). The variability of PaO_2 in each study period was expressed as the coefficient of variation (CV), which was defined as the SD/mean × 100. The intra-patient range was defined as the highest value obtained over the period minus the lowest value. Student's *t*-test

Table 2 Mean, SD, CV, and intra-patient range of PaO_2 for each patient at the three ventilatory settings (*CV* coefficient of variation)

Case	Setting A				Setting B				Setting C			
	Mean (kPa)	SD	CV (%)	Intra-patient range (kPa)	Mean (kPa)	SD	CV (%)	Intra-patient range (kPa)	Mean (kPa)	SD	CV (%)	Intra-patient range (kPa)
1	13.4	0.3	2.2	0.7	8.7	0.5	6.3	1.5	7.5	0.5	6.0	1.3
2	16.1	1.0	6.3	2.7	18.4	0.8	4.2	1.9	13.9	1.5	10.8	3.7
3	11.5	2.6	22.8	6.3	10.0	1.1	11.2	2.8	7.4	0.5	6.4	1.2
4	18.9	1.4	7.5	3.8	14.1	2.6	18.3	6.4	14.5	1.6	11.4	4.1
5	23.6	1.7	7.3	4.3	22.0	3.1	15.2	8.8	23.2	1.5	6.3	3.7
6	12.2	0.6	5.2	1.7	13.1	0.9	7.1	2.2	13.8	1.3	9.7	3.7
7	19.2	0.6	3.3	1.5	11.9	0.5	4.1	1.2	10.1	0.4	3.6	0.9
8	19.1	0.9	4.6	2.2	14.9	0.9	6.3	2.3	14.0	1.7	12.1	4.6
9	11.9	0.3	2.5	0.7	12.5	0.7	5.7	1.6	10.3	0.4	3.6	0.8
10	18.4	0.6	3.2	1.4	19.0	1.1	5.6	2.8	17.9	0.9	5.2	2.2
11	22.9	0.6	2.7	1.4	15.2	0.6	4.3	1.8	13.9	1.8	13.0	3.7
12	17.6	1.0	5.5	2.4	13.6	0.9	6.8	1.9	11.7	0.3	2.5	0.7
13	12.3	0.5	4.0	1.3	13.4	0.8	5.6	1.9	12.4	0.6	4.7	1.2
14	31.2	1.1	3.5	2.5	14.1	1.5	10.5	3.9	10.3	0.3	3.3	0.9
15	15.7	0.4	2.8	1.1	13.3	0.6	4.5	1.4	13.0	1.1	8.1	2.7
16	13.2	1.5	11.0	3.6	9.6	0.2	2.5	0.5	9.0	0.6	7.2	1.7
17	27.7	2.2	8.0	5.4	18.5	2.3	12.4	5.5	16.7	1.1	6.4	2.8
18	13.5	0.6	4.6	1.5	10.6	0.3	2.8	0.7	11.1	0.4	3.7	1.1
19	18.5	1.1	5.9	2.2	18.7	2.8	14.7	6.9	17.5	1.1	6.3	3.1
20	13.9	1.7	12.4	3.7	13.1	1.0	7.3	2.6	13.7	1.0	7.4	2.6
21	13.3	0.7	5.1	1.5	11.5	0.3	2.9	0.9	12.1	0.7	5.8	1.7
22	14.4	0.4	2.5	0.9	14.2	0.8	5.6	2.2	10.6	1.3	12.3	3.4
23	17.3	0.5	2.8	1.3	19.4	0.5	2.5	1.3	17.1	0.6	3.2	1.3
Mean	17.2		5.9		14.3		7.2		13.1		6.9	
SD	5.2		4.6		3.5		4.4		3.7		3.2	

was used to compare the magnitude of the CV from the Thorson et al. [4] and Sasse et al. [6] studies to that found in our patients. A p value less than 0.05 was considered significant. To compare the magnitude of the variability for the three ventilator settings, a repeated measures analysis of variance (ANOVA) was used. A paired samples t-test was applied for the pairwise comparison of the magnitude of variability of PaO_2 and the tension-based indices of oxygenation and venous admixture. For the multiple tests (four in total), the α error was adjusted according to the Bonferroni t procedure; therefore, only the results with a p value less than 0.0125 were considered significant.

Results

The mean, SD, CV, and intra-patient range of PaO_2 for each patient during the three setting periods are shown in Table 2. The PaO_2 of setting A ranged from 11.5 to 31.2 kPa (mean 17.2 ± 5.2 kPa), of setting B 8.7 to 22 kPa (mean 14.3 ± 3.5 kPa), and of setting C 7.4 to 23.2 kPa (mean 13.1 ± 3.7 kPa). The intra-patient range of setting A was 0.7 to 6.3 kPa (mean 2.3 ± 1.5 kPa), of setting B 0.5 to 8.8 kPa (mean 2.7 ± 2.2 kPa), and of setting C 0.7 to 4.6 kPa (mean 2.3 ± 1.2 kPa). The CVs of PaO_2 for setting A ranged from 2.2 to 22.8% (mean 5.9 ± 4.6%), for setting B 2.5 to 18.3% (mean 7.2 ± 4.4%), and for setting C 2.5 to 13% (mean 6.9 ± 3.2%). If we pooled together the mean PaO_2 and CV values of the three settings for all the patients, the pooled mean PaO_2 and mean CV were 14.9 kPa and 6.7%, respectively.

In Table 3, we show the mean values and mean CVs of heart rate, systolic and mean systemic and pulmonary artery pressures, and CO for patients at the three settings. The CVs of heart rate and systolic and mean systemic artery pressures at each ventilatory setting were all less than 5%. Therefore, we considered our patients to be hemodynamically stable under sedation.

The original CV values of PaO_2 for each patient in both the Thorson et al. and Sasse et al. studies were reported in their papers, allowing comparison with our

Table 3 The mean values and CVs of hemodynamic parameters and cardiac output *CO* at the three ventilatory settings (*CV* coefficient of variation, *HR* heart rate, *ABPs* systolic arterial blood pressure, *ABPm* mean arterial blood pressure, *PAPs* systolic pulmonary artery pressure, *PAPm* mean pulmonary artery pressure)

	HR (beats/min)		ABPs (mm Hg)		ABPm (mm Hg)		PAPs (mm Hg)		PAPm (mm Hg)		CO (l/min)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
Setting A	105 ± 16	2.71	142 ± 33	3.90	98 ± 22	4.06	39 ± 11	4.03	29 ± 7	5.41	5.6 ± 1.8	4.95
Setting B	98 ± 17	3.05	147 ± 32	4.12	100 ± 24	3.63	40 ± 13	5.28	28 ± 9	5.10	5.5 ± 1.4	5.75
Setting C	102 ± 18	3.19	145 ± 31	3.34	98 ± 21	3.52	40 ± 14	6.58	28 ± 8	6.20	6.0 ± 1.8	5.07

Table 4 The CVs of tension-based indices, and venous admixture Q_s/Q_t at the three ventilatory settings

	$A\text{-}aDO_2$ (kPa)		PaO_2/PAO_2		$A\text{-}aDO_2/PaO_2$		Q_s/Q_t (%)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
Setting A	15.6 ± 7.6	7.00	0.54 ± 0.15	5.75	1.03 ± 0.7	12.46	15 ± 7	10.31
Setting B	20.6 ± 9.8	6.61	0.43 ± 0.15	7.09	1.62 ± 1.05	13.76	18 ± 6	9.78
Setting C	21.5 ± 8.6	4.81	0.40 ± 0.14	6.64	1.86 ± 1.22	11.20	21 ± 9	9.53
Mean		6.08		6.58		12.46		9.78

data. Student's *t*-test revealed no significant difference in the CVs between any of our three setting periods and those of Thorson et al. or Sasse et al. Nor did ANOVAs show any significant differences between the CVs at the three settings ($p = 0.52$). Ventilator settings with either high PEEP or IRV did not show greater spontaneous variability than the setting with low PEEP with conventional I:E ratio.

Each patient's CVs for PaO_2, Q_s/Q_t, and tension-based indices of oxygenation at the three settings were averaged and used to compare the stability of these parameters. The mean values and mean CVs are listed in Table 4. Multiple comparisons of the data through a paired samples *t*-test with Bonferroni correction revealed that no significant difference existed between the mean variability of PaO_2 and that of $A\text{-}aDO_2$ and PaO_2/PAO_2. The mean variability of $A\text{-}aDO_2/PaO_2$ and Q_s/Q_t was significantly greater than that of PaO_2, $A\text{-}aDO_2$, and PaO_2/PAO_2, and $A\text{-}aDO_2/PaO_2$ had the greatest variability of these five indices. PaO_2/FIO_2 had the same variability as PaO_2 because the FIO_2 during each study period was fixed.

A 95% confidence interval was used to describe the expected range of the mean PaO_2 value. The interval represents a range from 2 SDs below to 2 SDs above the mean value: 2 SDs equals 2 x CV x mean PaO_2 [24]. Thus, for a mean PaO_2 determination, the 95% confidence interval represents a range between mean $PaO_2$2 x CV x mean PaO_2. For the overall pooling group with a mean CV value of 6.7%, the 95% confidence interval equals mean $PaO_2 \pm 0.134$ x mean PaO_2. The 95% confidence intervals were mean $PaO_2 \pm 0.118$ x mean PaO_2 for setting A (CV 5.9%), mean $PaO_2$0.144 x mean PaO_2 for setting B (CV 7.2%), and mean $PaO_2 \pm 0.138$ x mean PaO_2 for setting C (CV 6.9%).

Discussion

The topic of spontaneous variability over time of ABG values has been previously discussed by Thorson et al., Hess et al. and Sasse et al. [4–6]. Except for placing their patients in a supine position to decrease spontaneous activities, no sedation was administered in their studies to eliminate external environmental influences. Patients in both the Thorson et al. and the Sasse et al. studies [4, 6] were receiving mechanical ventilation or were breathing spontaneously, and all the patients in the Hess and Agarwal study [5] received mechanical ventilation. The ventilatory modes mentioned included assist/control, intermittent mandatory ventilation (IMV) or synchronized IMV, or continuous positive airway pressure. The time interval for blood gas samp ling and the total number of specimens were: 10-min intervals/6 specimens in the Thorson et al protocol. [4], 20-min intervals/4 specimens in Hess and Agarwal's protocol [5], and 5-min intervals/13 specimens in the Sasse et al. protocol [6]. The mean CVs for PaO_2 were 5.3, 4.6, and 6.1%, respectively. Although some differences existed between their studies, all these authors discovered substantial spontaneous variability in PaO_2 over short time intervals, even in stable ICU patients who had not experienced therapeutic intervention or showed observable clinical changes. All concluded that spontaneous variability should be taken into account when basing clinical decisions on blood gas values.

The spontaneous variability in PaO_2 consists of preanalytic variability, individual patient variability, and analytic variability [5]. The preanalytic errors in blood gas analysis specifically concern: (1) air contamination, (2) improper storage, (3) heparin dilution, (4) venous puncture, and (5) contamination of the arterial line solution [25]. In order to minimize probable preanalytic errors, all the blood gas samples were collected from the arterial catheter by only the author and one nurse according to the aforementioned principles. Analy tic variability related to the blood gas analyzer was avoided by performing regularly scheduled quality control and proper calibration according to the manufacturer's recommendations. The most important difference between our study and previous studies was the use of sedation to decrease individual patient variability.

To investigate the actual spontaneous variability of PaO_2, influences such as muscular activity, pain, arousal, metabolic O_2 demand, emotional changes, (e.g., anxiety, agitation, and stress), and fluctuation in the amount of ventilation must be minimized. This principle was reflected in the results of the Sasse et al. study [6]. Although it was not statistically significant, spontaneously breathing patients showed a trend toward greater variability in PaO_2 (mean CV 6.5 %) than mechanically ventilated patients (mean CV 5.2 %). In contrast, our patients were all completely sedated during the study periods. By using sedation, we greatly eliminated extraneous and intrinsic interference. The small CVs of heart rate and blood pressure confirm the stable hemodynamics in our patients (Table 3).

Despite our special effort to minimize individual variability, the CVs of PaO_2 at the three ventilatory settings in our study (Table 2) were not less than in previous reports. The clinical diagnoses of our patients represented disease categories requiring insertion of a pulmonary artery catheter for CO monitoring (e.g., shock, renal failure, and pulmonary infiltrates with hypoxia [26]), essentially the most critically ill group in a medical ICU. We speculate that, although not significantly different than those in the Thorson et al. and Sasse et al. studies [4, 6], the greater severity in our patients resulted in greater fluctuations in PaO_2 over time.

For severely hypoxemic patients or for ARDS, maintaining adequate tissue oxygenation and reverse tissue hypoxia are essential to prevent the occurrence of multiple system organ failure. Many agree that high level PEEP and IRV can recruit collapsed alveoli, reduce ventilation-perfusion mismatch, decrease intrapulmonary shunt, and improve arterial oxygenation [7–10]. However, both settings will result in greater changes in intrathoracic pressure over the respiratory cycle. The higher mean airway pressure will compromise the CO and hemodynamics, which, in turn, will alter the pulmonary ventilation-perfusion relationship. Probably, both A and B settings will show higher fluctuations in PaO_2 than setting C. However, we found no significant difference among the CVs of PaO_2 for the three setting periods. The more sophisticated mechanical ventilatory settings we depend on to overcome severe hypoxemia did not cause a greater spontaneous variability in PaO_2.

The oxygen tension-based indices have been introduced as convenient alternatives to physiological shunt fraction (Q_s/Q_t) as a means of reflecting disturbances in pulmonary oxygen transfer when mixed venous blood sampling is not available. Among these tension-based indices, Hess and Maxwell [15] suggested that PaO_2/PAO_2 is a relatively sensitive indicator of pulmonary dysfunction and seems to be more reliable than A-aDO_2 and PaO_2/FIO_2 with changes in FIO_2. However, if FIO_2 is not changed, PaO_2, A-aDO_2, PaO_2/FIO_2, and PaO_2/PAO_2 are equally suitable for serial assessments of the efficiency of pulmonary oxygenation because the spontaneous variability of PaO_2, A-aDO_2, and PaO_2/PAO_2 is similar (Table 4).

The highest variation in A-aDO_2/PaO_2 is reasonable because, in its calculation, it inherits the changes coming from both A-aDO_2 and PaO_2. In pressure control mode, although the driving pressure (peak pressure-PEEP gradient) is fixed, the tidal volume is still variable and subject to changes in pulmonary mechanical properties. In addition, intrathoracic pressures and CO fluctuate along with the cyclic changes in positive pressure ventilation [27]. Both the systolic and mean pulmonary artery pressures and CO in our study displayed much higher spontaneous variabi lity than systemic artery pressures indicating that the amount of pulmonary perfusion also changes greatly with time (Table 3). It is conceivable that both the fluctuations from pulmonary perfusion and ventilation result in a high variation in Q_s/Q_t.

Under complete sedation, the mean CV of PaO_2 over a 1-h period in the overall pooled group and at settings A, B, and C were 6.7, 5.9, 7.2, and 6.9 %, respectively (Table 2). Therefore, the expected range of variability around the mean PaO_2 for the overall pooled group (i.e., the 95 % confidence interval) was mean $PaO_2 \pm 0.134$ x mean PaO_2. The 95 % confidence interval was mean $PaO_2 \pm 0.118$ x mean PaO_2 for setting A, mean $PaO_2 \pm 0.144$ x mean PaO_2 for setting B, and mean $PaO_2 \pm 0.138$ x mean PaO_2 for setting C. Given a mean PaO_2 of 10 kPa, the 95 % confidence interval for the overall pooled group was 8.66 to 11.34 kPa. For setting A, it was 8.2 to 11.8 kPa, for setting B 8.56 to 11.44 kPa, and for setting C 8.62 to 11.38 kPa. Therefore, the 95 % confidence interval for our patients may be simplified to mean $PaO_2 \pm 0.15$ x mean PaO_2. The 95 % confidence interval signifies that patients will achieve either an improvement in PaO_2 due to treatment interventions or a deterioration in arterial oxygenation from worsening disease or inappropriate ventilatory support, when changes in PaO_2 exceed these ranges.

In conclusion, we found that in medical ICU patients, even under sedation to minimize intrinsic and extraneous interference, the spontaneous variability of PaO_2 over time is substantial. More sophisticated ventilatory supports, such as high PEEP (15 cmH_2O) or inverse I:E ratio ventilation (2:1), do not contribute to a greater spontaneous variation in PaO_2 than low PEEP (5 cmH_2O) with conventional I:E ratio ventilation (1:2). The oxygen tension-based indices A-aDO_2 and PaO_2/PAO_2 are equally stable with PaO_2 when used for serial evaluations of pulmonary oxygenation at separate times with the same FIO_2. However, special caution is needed when Q_s/Q_t and A-aDO_2/PaO_2 are used for evaluation of pulmonary dysfunction because of their greater fluctuation over time. Finally, a magnitude of change in PaO_2 of less than 0.15 x mean PaO_2 measured does not necessary signify a meaningful change but may be due to spontaneous individual variation. We corroborate the argument of Thorson et al. [4] that therapeutic decisions should be based on trends in PaO_2 rather than on isolated changes interpreted without appropriate clinical correlations.

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