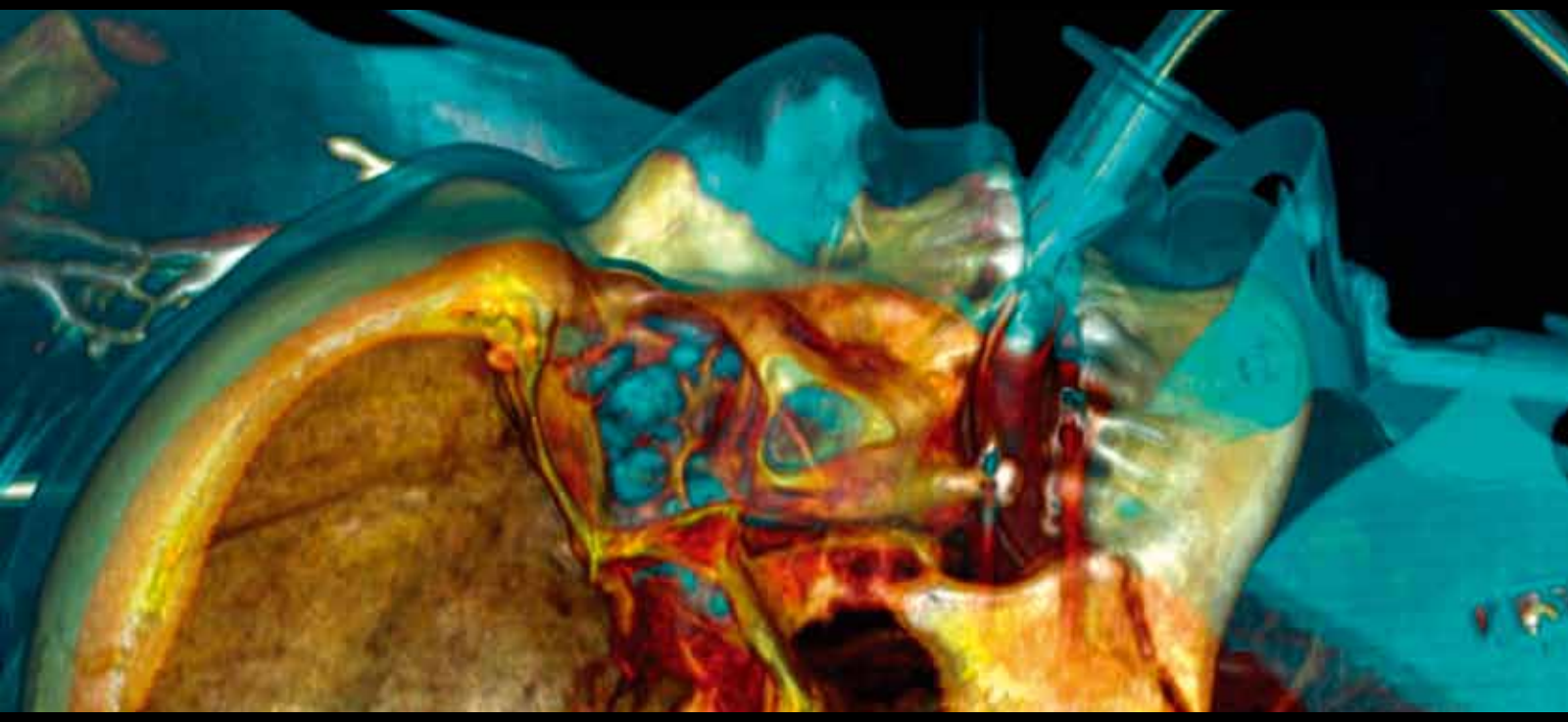
Critical Care Research and Practice

Goal-Directed Therapy: New Trends and Horizons

Guest Editors: Mikhail Kirov, Lars Bjertnaes, Zsolt Molnar, and Samir Sakka



Goal-Directed Therapy: New Trends and Horizons

Critical Care Research and Practice

Goal-Directed Therapy: New Trends and Horizons

Guest Editors: Mikhail Kirov, Lars Bjertnaes, Zsolt Molnar, and Samir Sakka

Editorial Board

Contents

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 576253, 1 page
doi:10.1155/2012/576253

Editorial

Goal-Directed Therapy: New Trends and Horizons

Mikhail Kirov,[1] Lars Bjertnaes,[2,3] Zsolt Molnar,[4] and Samir Sakka[5]

[1] *Department of Anesthesiology and Intensive Care Medicine, Northern State Medical University, Troitsky Avenue 51, Arkhangelsk 163000, Russia*
[2] *Department of Anesthesiology, University Hospital of North Norway, Tromsø, Norway*
[3] *Anesthesia and Critical Care Research Group, Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, 9037 Tromsø, Norway*
[4] *Department of Anaesthesiology and Intensive Therapy, Faculty of Medicine, University of Szeged, Szeged, Hungary*
[5] *Department of Anesthesiology and Intensive Therapy, Cologne-Merheim Medical Center, University of Witten/Herdecke, Krankenhaus Merheim Ostmerheimer Str. 200, 51109 Cologne, Germany*

Correspondence should be addressed to Mikhail Kirov, mikhail_kirov@hotmail.com

Received 1 October 2012; Accepted 1 October 2012

In traumatized or critically ill patients suffering from a variety of severe illnesses, survival often depends on the successful handling of a chain of time-critical events with the ultimate goal to provide sufficient tissue oxygenation. Timely initiated goal-directed therapy (GDT) is a cornerstone in the care and treatment of these patients. Based on adequate monitoring techniques, goal-directed algorithms can facilitate the early detection of pathophysiological changes and influence therapies that may improve the clinical outcomes [1]. However, there are still many controversies regarding the application of GDT in different categories of patients [2]. Thus, a search for critical illnesses and conditions that might potentially profit from GDT may be of significant importance.

In this special issue we have invited authors to submit original research and review articles elucidating the front of research and defining the optimal targets for the management and treatment of various perioperative and critically ill conditions, subsequently describing goal-oriented therapeutical interventions. The papers represent a wide spectrum of topics including early hemodynamic therapy in sepsis, perioperative monitoring, goal-directed hemodynamic optimization in cardiothoracic surgery, goal-oriented management of mechanical ventilation in respiratory failure, and important aspects of novel therapies in acute lung injury and acute respiratory distress syndrome. The publications reflect new therapeutic approaches for many critically ill patients. New targets for GDT and treatment algorithms are elucidated, such as static and dynamic preload parameters, weaning and derecruitment tests during ventilation, esophageal pressure, and other respiratory variables. The papers also reflect the limitations of current monitoring tools and therapeutic strategies and discuss the optimal indications of their use.

We hope that the articles in this special issue will create new ideas of goal-directed therapies that can be evaluated for future clinical implementation.

Mikhail Kirov
Lars Bjertnaes
Zsolt Molnar
Samir Sakka

References

[1] M. Y. Kirov, V. V. Kuzkov, and Z. Molnar, "Perioperative haemodynamic therapy," *Current Opinion in Critical Care*, vol. 16, no. 4, pp. 384–392, 2010.

[2] M. Cannesson, G. Pestel, C. Ricks, A. Hoeft, and A. Perel, "Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists," *Critical Care*, vol. 15, p. R197, 2011.

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 204314, 8 pages
doi:10.1155/2012/204314

Research Article

Human versus Computer Controlled Selection of Ventilator Settings: An Evaluation of Adaptive Support Ventilation and Mid-Frequency Ventilation

Eduardo Mireles-Cabodevila,[1,2] Enrique Diaz-Guzman,[3] Alejandro C. Arroliga,[4] and Robert L. Chatburn[2]

[1] *Department of Pulmonary and Critical Care Medicine, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot 555, Little Rock, AR 77205, USA*
[2] *Respiratory Institute, Cleveland Clinic, 9500 Euclid Avenue, A90, Cleveland, OH 44195, USA*
[3] *Department of Pulmonary and Critical Care, University of Kentucky, Lexington, KY 40536-0284, USA*
[4] *Department of Medicine, Scott and White and Texas A and M Health Science Center College of Medicine, 2401 South 31st Street, Temple, TX 76508, USA*

Correspondence should be addressed to Eduardo Mireles-Cabodevila, mirelee@ccf.org

Received 24 May 2012; Accepted 7 September 2012

Academic Editor: Samir Sakka

Background. There are modes of mechanical ventilation that can select ventilator settings with computer controlled algorithms (targeting schemes). Two examples are adaptive support ventilation (ASV) and mid-frequency ventilation (MFV). We studied how different clinician-chosen ventilator settings are from these computer algorithms under different scenarios. *Methods*. A survey of critical care clinicians provided reference ventilator settings for a 70 kg paralyzed patient in five clinical/physiological scenarios. The survey-derived values for minute ventilation and minute alveolar ventilation were used as goals for ASV and MFV, respectively. A lung simulator programmed with each scenario's respiratory system characteristics was ventilated using the clinician, ASV, and MFV settings. *Results*. Tidal volumes ranged from 6.1 to 8.3 mL/kg for the clinician, 6.7 to 11.9 mL/kg for ASV, and 3.5 to 9.9 mL/kg for MFV. Inspiratory pressures were lower for ASV and MFV. Clinician-selected tidal volumes were similar to the ASV settings for all scenarios except for asthma, in which the tidal volumes were larger for ASV and MFV. MFV delivered the same alveolar minute ventilation with higher end expiratory and lower end inspiratory volumes. *Conclusions*. There are differences and similarities among initial ventilator settings selected by humans and computers for various clinical scenarios. The ventilation outcomes are the result of the lung physiological characteristics and their interaction with the targeting scheme.

1. Introduction

The evolution of the computerized control of mechanical ventilators has reached the level where the ventilator can select some (previously human selected) settings based on computer controlled targeting schemes [1–4]. One of these control algorithms is called an "optimum targeting scheme" for which the only commercially available mode is adaptive support ventilation (ASV). "Optimum", in this context means to minimize the work rate of breathing a patient would have to do if breathing unassisted with the ventilator selected tidal volume and frequency [5, 6]. These settings are based on the ventilator's assessment of respiratory system characteristics (i.e., alveolar minute ventilation requirement, estimated dead space volume, and expiratory time constant). Although ASV has embedded rules that attempt to prevent hypoventilation, air trapping, and volutrauma, the primary goal is not the prevention of lung injury. ASV has been reported to choose ventilator settings that provide adequate ventilation in patients with a variety of clinical conditions [7–9].

We developed mid-frequency ventilation (MFV) [10], a mode of ventilation using an optimum targeting scheme with the goal of maximizing alveolar ventilation and minimizing

tidal volume to promote lung protection. The theoretical basis for MFV has been described elsewhere [10]. In brief, MFV uses a mathematical model for pressure control ventilation where patient characteristics (alveolar minute ventilation requirement, dead space ratio, and inspiratory, and expiratory time constants) are used to calculate optimal frequency and tidal volume settings. In this case, optimum is defined as the frequency and tidal volume that produce the maximum alveolar minute ventilation for a given inspiratory pressure setting (above PEEP). MFV results in higher ventilator frequencies delivering the lowest tidal volume possible for a given target minute ventilation and inspiratory pressure, while using a conventional ventilator.

In order to allow a computer to choose ventilator settings, the clinician, must trust the process by which these settings are determined. Although several studies have been published with ASV, [1, 8, 9, 11, 12] none compared them directly to human performance. The purpose of this study was to compare the initial ventilator settings selected by human operators with those selected by two computer algorithms (ASV and MFV) in five hypothetical clinical scenarios.

2. Materials and Methods

The study was divided into 2 steps. The first step was to determine the clinician-selected ventilator settings. A survey was made available to all the medical and surgical critical care physicians, fellows, and respiratory therapists at the Cleveland Clinic. The survey asked for proposed ventilator settings for five hypothetical patient scenarios. The second step was to evaluate the ventilation outcomes (tidal volume, lung volumes, and airway pressures). We used a lung simulator programmed with the scenarios' respiratory system characteristics ventilated with the clinician-selected settings, ASV, and MFV.

2.1. First Step: Electronic Survey. The Institutional Review Board approved the survey. An electronic survey (http://www.surveymonkey.com/, Portland, OR) was sent by email to faculty and fellows and posted in the respiratory therapy website from December 1 to 31, 2007. The survey presented five clinical scenarios (Table 1). All the scenarios used the same baseline parameters: a 70 kg predicted body weight, male, paralyzed. The scenarios included a patient with normal lungs, two patients with restrictive disorders (ARDS and morbid obesity), and two with obstructive lung disease (COPD and status asthmaticus). The scenarios were hypothetical, and included arterial blood gases (validity confirmed by the Henderson-Hasselbalch formula [13]); ventilator settings in volume controlled continuous mandatory ventilation and previously published values for lung resistance and compliance for each condition (Table 1). The survey asked what ventilator settings the clinician would choose for each scenario. The options were tidal volume goal, respiratory rate, I : E ratio, and PEEP.

We only used the results from surveys that had all answers completed. The survey results were used to calculate the clinician goal for minute ventilation (respiratory rate multiplied by tidal volume) and alveolar minute ventilation (tidal volume minus dead space volume (estimated as 2.2 mL/kg) multiplied by respiratory rate). A fixed dead space volume was used in all clinical scenarios to fully appreciate the effects of the settings.

2.2. Second Step: Lung Simulator. We used a lung simulator (Ingmar ASL 5000, IngMar Medical Ltd., Pittsburgh, PA) to recreate the clinical scenarios in the survey. The simulator was set up as a passive respiratory system composed of a single linear constant resistance and single constant compliance. The respiratory system compliances and resistances used in the survey were programmed for each clinical scenario (Table 1). The parameters were constant during the experiments. Data from the simulator were recorded in a high-resolution file (500 Hz sampling frequency). Tidal volumes and end inspiratory and end expiratory volumes were measured as the excursion of the piston inside the lung simulator.

Two mechanical ventilators were used: a Hamilton Galileo, (Hamilton Medical AG, Bonaduz, Switzerland) to deliver clinician settings (with pressure control ventilation) and ASV and a Dräger Evita XL (Dräger Medical AG & Co., Lübeck, Germany) to deliver MFV. The change in ventilator to deliver the MFV was due to our previous experience [10] that showed the Dräger ventilator generating the sharply rectangular pressure waveform necessary for efficient MFV. The ventilators were connected to the lung simulator using a conventional circuit (70 inches long) with separate inspiratory and expiratory limbs (Airlife; Cardinal Health, McGaw Park, IL) without a humidifier chamber. All experiments were conducted using room air ($F_IO_2 = 0.21$) and reported as measured. The ventilators were calibrated and tested for leaks prior to the experiments.

2.3. Experimental Protocol

2.3.1. Clinician Settings. For each of the clinical scenarios we obtained the average tidal volume, respiratory rate, I : E ratio, and PEEP selected in the survey. The ventilator was set with these values.

To maintain comparability with MFV and ASV (both pressure controlled modes), clinician ventilator settings were delivered with pressure controlled continuous mandatory ventilation (i.e., all breaths were time triggered, pressure limited, and time cycled). Inspiratory pressure was determined in a preliminary run on the simulator to achieve the target tidal volume. Pressure rise time was set to the minimum available on each ventilator (Hamilton 50 ms, Dräger 0 ms).

2.3.2. Adaptive Support Ventilation. The ventilator was programmed for ventilation on an adult male patient. The height was set at 174 cm, which represents 70 kg of predicted body weight. For each case scenario, the percent minute ventilation was set to achieve the target minute ventilation obtained from the clinician survey. ASV was maintained

Table 1: Clinical scenarios.

Clinical Scenario	Acid-base and oxygenation status	Compliance mL/cm H_2O	Resistance cm H_2O/L/S
Healthy patient undergoes surgical repair of the knee. He has a rare enzymatic defect that prolonged the paralytic half-life and will require mechanical ventilation until paralysis wears off.	*Normal acid-base status*. ABG: pH 7.40, $PaCO_2$ 40, HCO_3 of 24, and PaO_2 90 on a 30% FiO_2	**66**	**4**
ARDS due to severe sepsis. Current ventilation: VC-CMV, V_T 550, RR 28, FiO_2 65%, PEEP of 12.	*Metabolic and respiratory acidosis.* ABG: pH 7.25, $PaCO_2$ 42, HCO_3 of 18 and PaO_2 65 on a 65% FiO_2	**25**	**10**
Morbid obesity: weight is 200 kg, he has opiate overdose. He is paralyzed due to high ventilator pressures. Current ventilation: VC-CMV, V_T 650, RR 18, FiO_2 35%, PEEP of 8.	*Respiratory acidosis.* ABG: pH 7.27, $PaCO_2$ 85, HCO_3 of 38 and PaO_2 65 on a 35% FiO_2.	**35**	**12**
COPD: has a broken hip, intubated for surgery. Current ventilation: VC-CMV, V_T 700, RR 12, FiO_2 35%, PEEP of 8, and I : E 1 : 4.	*Respiratory alkalosis.* ABG: pH 7.53, $PaCO_2$ 42, HCO_3 of 34 and PaO_2 65. No auto PEEP is detected.	**60**	**16**
Status asthmaticus: paralyzed in the ED to facilitate ventilation. Current ventilation: VC-CMV, V_T 600, RR 22, FiO_2 35%, PEEP of 10, I : E is 1 : 2.	*Severe respiratory acidosis.* ABG: pH 7.12, $PaCO_2$ 75, HCO_3 of 24 and PaO_2 65 on a 35% FiO_2. Auto PEEP is 6.	**80**	**Inspiratory 16 Expiratory 22**

VC-CMV: Volume control-continuous mandatory ventilation, V_T: tidal volume, RR: respiratory rate (breaths per minute), I : E: inspiratory : expiratory ratio, PEEP: positive end expiratory pressure (cm H_2O), ABG: arterial blood gas. $PaCO_2$: arterial partial pressure of CO_2 (mmHg), PaO_2: arterial partial pressure of O_2 (mmHg), FiO_2: inspired fraction O_2. References: healthy paralyzed [14], ARDS [15, 16], morbid obesity [14], COPD [15], status asthmaticus [17].

Table 2: Survey results.

Condition	Tidal volume mL	Tidal volume mL/kg (*)	Alveolar volume mL	RR bpm (*)	PEEP cm H_2O	I : E ratio (DC)	MV calc L/min	MV_A calc L/min
Normal lungs/normal acid-base	535 ± 89	7.6 (5.7–10)	382	12 ± 3 (8–23)	5 ± 1	1 : 3 (25)	6.4	4.6
ARDS/mixed acidosis	428 ± 38	6.1 (5–7.1)	275	27 ± 7 (10–42)	12 ± 2	1 : 1.5 (40)	11.6	7.4
Obesity/respiratory acidosis	578 ± 105	8.3 (5.7–11.4)	425	21 ± 3 (12–30)	8 ± 2	1 : 2 (33)	12.1	8.9
COPD/respiratory alkalosis	536 ± 80	7.7 (5.7–10)	383	11 ± 2 (6–16)	7 ± 2	1 : 4 (20)	5.9	4.2
S. asthmaticus/respiratory acidosis	542 ± 102	7.7 (5.7–11.4)	389	20 ± 6 (6–30)	9 ± 4	1 : 4 (20)	10.8	7.8

Values are expressed as mean ± SD or mean alone. (*): range. Tidal volume per kg of predicted body weight (70 kg), alveolar volume was calculated by subtracting 153 mL (2.2 mL/Kg) dead space volume from the average tidal volume. BPM: breaths per minute. DC: duty cycle or percent inspiration. PC mode choice includes adaptive PC, PC-CMV, and IMV. MV: minute ventilation. MV_A: alveolar minute ventilation. PEEP: positive end expiratory pressure.

until ventilation parameters were stable (no change in tidal volume, respiratory rate or inspiratory pressure).

2.3.3. Mid-Frequency Ventilation. MFV uses pressure control continuous mandatory ventilation, with constant I : E ratio as frequency is changed. The ventilation parameters obtained from the computerized model for MFV [10] were used to program the ventilator to achieve the target alveolar ventilation.

The target minute ventilation used to set ASV and target alveolar ventilation used to set MFV are shown in Table 2. The values for initial ventilator settings for MFV are reported in Figure 1.

2.3.4. PEEP. Note that the survey asked for PEEP values, and these were used to set the ventilator and the model. However, contrary to clinical practice, PEEP has no effect on the lung simulator's behavior. More to the point, none of the computerized systems calculates or sets PEEP. Hence, the comparison between human and computer selection of ventilator settings is focused on frequency and tidal volume and ventilation outcomes.

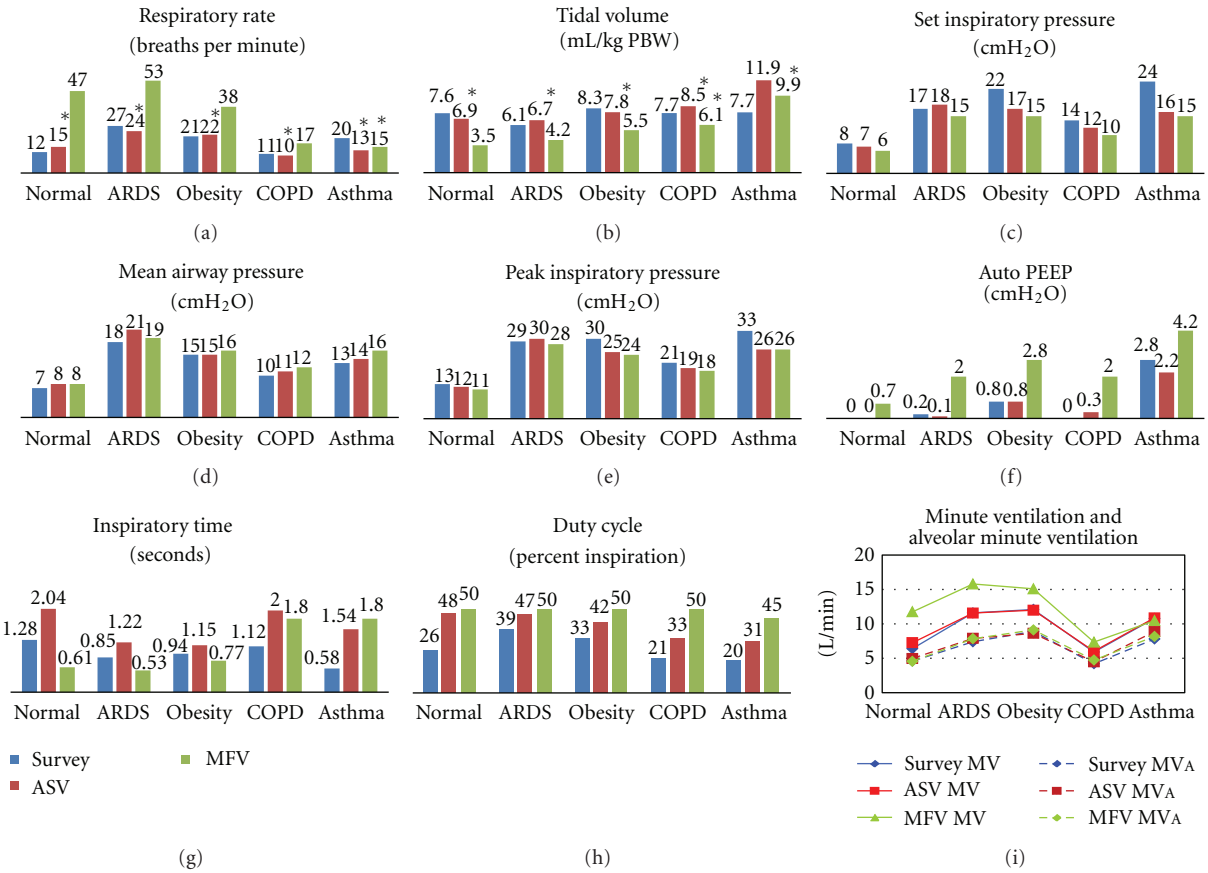


Figure 1: Clinician-selected settings, adaptive support ventilation and mid-frequency ventilation applied to lung simulator. (a) Respiratory rate; (b) tidal volume as registered by the lung simulator; (c) set inspiratory pressure above PEEP needed to deliver target tidal volume; (d) mean airway pressure; (e) peak inspiratory pressure; (f) auto PEEP; (g) inspiratory time; (h) duty cycle or percent time in inspiration; (i) exhaled minute ventilation (MV) and calculated alveolar minute ventilation (MV_A). Values measured by the lung simulator: (b, d, e, g, h, and i). *Value within the range obtained from the clinician survey.

3. Statistical Analysis

Results were analyzed with JMP IN (SAS, Cary, NC). The survey results are reported as mean and standard deviation. The results and respective comparisons between groups on the lung model are only descriptive. The lung model generates values with virtually zero standard deviation; hence, only descriptive statistics are reported.

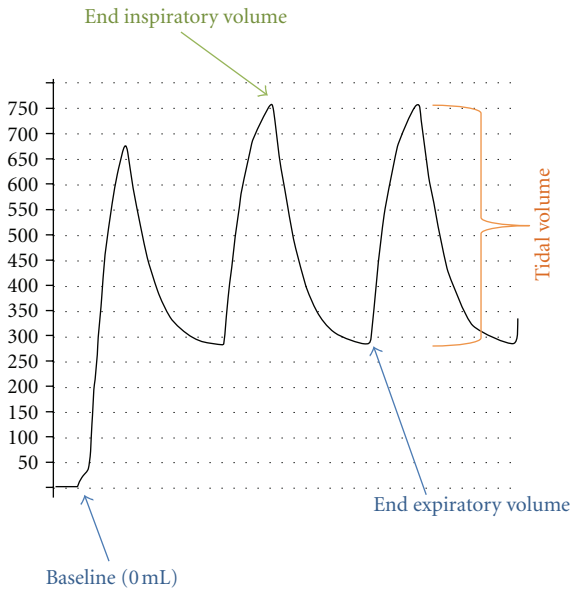
4. Results

4.1. Clinician Settings Survey Results. The electronic survey was available to 176 respiratory therapist, fellows, and staff from the medical, surgical, and cardiothoracic intensive care units of the Cleveland Clinic. A total of 54 surveys were collected at the end of the study period. Of these, only 33 were completely answered (13 (39%) critical care staff, 6 (18%) critical care fellows, and 14 (42%) intensive care respiratory therapist) and were used to obtain the reference values.

Table 2 depicts the results of the survey and the calculated minute ventilation and alveolar ventilation. Tidal volumes ranged from 6.1 mL/kg (ARDS) to 8.3 mL/kg (morbid obesity). Clinicians reduced tidal volumes (range 0.9 to 2.3 mL/kg) from the tidal volume used in the scenario. In the obstructive lung disease scenarios, clinicians decreased respiratory rate on average 1 to 2 breaths per minute.

The minute ventilation calculated from survey response was in accordance with the acid-base disorder (i.e., an increase in minute ventilation for acidosis and a decrease for respiratory alkalosis). The clinicians' selected minute ventilation (6.4 L/min) was similar to the calculated normal minute ventilation (7.0 L/min) for a healthy patient >15 kg (i.e., 100 mL/kg/min ideal body weight) [5].

4.2. Survey Results, Adaptive Support Ventilation, and Mid-Frequency Ventilation Applied on to a Lung Simulator. Figure 1 shows the results of the survey, ASV, and MFV when applied to the lung simulator. The tidal volume selected was 6.7 to 11.9 mL/kg for ASV, and 3.5 to 9.9 mL/kg for MFV. The difference between ASV and the clinician-selected tidal volumes was negligible (−0.9 to 0.7 mL/kg), with the exception of status asthmaticus where tidal volume selected by ASV was 3.9 mL/kg (55%) larger. MFV selected tidal



Lung volumes					
	End inspiratory volume (mL/Kg)				
	Survey	ASV	MFV	%diff[1]	%diff[2]
Normal	12.1	11.5	8.5	−5	−30
ARDS	10.3	10.9	9.1	5	−11
Obesity	12.3	11.9	10.9	−4	−12
COPD	13.8	14.6	13.7	6	−1
Asthma	21.2	24.4	24.7	15	17
	Tidal volume (mL/Kg)				
	Survey	ASV	MFV	%diff[1]	%diff[2]
Normal	7.6	6.9	3.5	−9	−54
ARDS	6.1	6.7	4.2	10	−31
Obesity	8.3	7.8	5.5	−6	−34
COPD	7.7	8.5	6.1	10	−21
Asthma	7.7	11.9	9.9	55	29
	End expiratory volume (mL)				
	Survey	ASV	MFV	%diff[1]	%diff[2]
Normal	4.5	4.6	4.8	2	6
ARDS	4.6	4.3	4.9	−7	8
Obesity	4.3	4.3	5.4	0	26
COPD	6.2	6.2	7.6	0	24
Asthma	13.5	12.8	15.1	−5	12

%diff[1]: percent difference between survey and ASV
%diff[2]: percent difference between survey and MFV

Figure 2: Lung volumes and ventilator settings. End inspiratory and expiratory volumes are total volumes normalized by weight as measured from the baseline. Baseline is 0 mL in the lung simulator; hence, end expiratory volume is a reflection of PEEP and aPEEP and the end inspiratory volume is a manifestation of PEEP, aPEEP, and tidal volume. Tidal volume was measured as the excursion of the simulator piston; however, it can also be estimated by subtracting the end expiratory from the end inspiratory volumes.

volumes that were 1.5 to 4.1 mL/kg lower than the clinician-selected tidal volumes, with the exception of asthma, were MFV selected tidal volumes were larger (2.2 mL/kg). MFV used higher respiratory rates and lower tidal volumes. This was most evident in normal and restrictive physiology. In obstructive scenarios, both ASV and MFV used lower respiratory rates (in status asthmaticus even lower than the clinicians) combined with longer inspiratory times (a result of larger duty cycles).

Figure 1(i) compares the calculated minute ventilation with the one delivered by MFV and ASV. Of note is how calculated alveolar ventilation goals were equal with each mode.

Figure 2 depicts the effects and differences in lung volumes between ventilator settings. With the exception of asthma, ASV had very similar (within 6%) end inspiratory volumes (EIV) and end expiratory volumes (EEV) to the clinician survey. MFV had 6–12% larger EEV, but when coupled with lower tidal volumes resulted in 1–30% less EIV. In the asthma scenario, both computer algorithms had larger EIV (15% ASV and 17% MFV) than the clinicians.

Mean airway pressures (mP_{AW}) were similar for all strategies (within 3 cm H_2O), with a trend towards higher values in MFV (probably due to the more rectangular pressure waveform of the Dräger ventilator compared to the Hamilton ventilator). Peak inspiratory pressure tended to be lower with the computer algorithms; this difference was small (within 3 cm H_2O) with the exception of obesity and asthma where the difference was more evident (≈6 cm H_2O). MFV used less inspiratory pressure for all scenarios than ASV and the clinician settings. AutoPEEP (aPEEP) was identical between ASV and the clinician-selected values and was essentially nonexistent with the exception of asthma. MFV had consistently higher (≈2 cm H_2O) aPEEP than the other strategies. The duty cycle was higher in MFV and ASV for all scenarios; however, because of the high respiratory rate in restrictive and normal lungs the inspiratory times were usually shorter for MFV.

5. Discussion

Our study demonstrates the differences between the clinician's settings and closed loop targeting schemes. These differences may not be significant in some cases. For example, ASV yields ventilation settings and ventilation outcomes very similar to clinician's choice and published guidelines for scenarios as ARDS and normal lungs but not for obstructive disorders. While, MFV results in less volume (both tidal volume and end inspiratory volume) and pressure (for most scenarios) than either ASV or clinicians.

ASV and MFV are examples of optimal control targeting schemes for mechanical ventilators [18]. Yet the modes have different optimization goals: ASV's optimum settings aim to minimize the work rate of breathing, while MFV's goal is

to maximize alveolar ventilation and minimize tidal volume. MFV is not currently available as a mode on ventilators, so there are no published studies of clinical outcomes. Studies have evaluated ASV as the sole mode of ventilation [9], or in patients with stable gas exchange (without reporting baseline ventilator settings) [8], or had a specific protocols to set the comparator ventilator settings (fixed tidal volume, SIMV) regardless of lung disease or mechanics [19–21] or where done with ASV prototypes [1, 11]. Our study eliminated variability by utilizing the minute ventilation goals chosen by clinicians to set two optimal control modes. These yielded information on the effects of current ventilation strategies and those of computerized models.

In normal lung physiology, ASV chosen ventilator settings were similar to the clinician's choice and tidal volume (6.9 mL/kg) was within the range considered to be lung protective. MFV used 54% less tidal volume (3.5 mL/kg) which was associated with a 30% reduction in end inspiratory volume. Interestingly, there was minimal difference in aPEEP, PIP, and mP_{AW} amongst the three settings.

In ARDS, the tidal volume used by ASV was 0.6 mL/kg (10%) higher than the clinician's choice, well within range considered to be lung protective [22, 23]. The ASV algorithm uses >1 respiratory time constant to set the inspiratory time [5] which led to longer inspiratory times and thus contributed to a higher mP_{AW} compared to the clinicians. In the obesity scenario, where compliance and resistance were higher, ASV used lower tidal volume (0.5 mL/kg) with slightly longer inspiratory time resulting in the similar airway pressure. In comparison, in both restrictive disorders, MFV used higher than normal respiratory rates to deliver 31–34% lower tidal volumes than clinicians, resulting in an EEV 8–26% higher (recruitment) and 11-12% lower EIV (stretching). The combination of low EIV and high EEV, especially in restrictive lung disorders, are in concordance with MFV goal to maximize lung protection, that is, preventing atelectrauma and alveolar stretching.

In obstructive disorders, clinicians used different patterns of ventilation for COPD (low tidal volume/low respiratory rate) and status asthmaticus (low tidal volume/high respiratory rate) while the computerized models used the same pattern (large tidal volume/low respiratory rates) for both scenarios. Our results are in concordance with the ventilator setting patterns found by Arnal et al. [9] and Belliato et al. [8] in COPD (they did not report patients with status asthmaticus). The discrepancy in the clinician's ventilation pattern choice for obstructive disease can be explained by three situations. First, the COPD scenario depicted a patient with respiratory alkalosis due to overventilation, which intuitively required less minute ventilation, compared with severe respiratory acidosis in status asthmaticus (requiring an improvement not only in MV but also in gas exchange). Second, clinicians are used to managing respiratory failure due to COPD, not status asthmaticus. The reduction in cases of status asthmaticus requiring mechanical ventilation [24] may have led clinicians to become less familiar with the management of this condition. The goal of ventilator management in status asthmatics has been to prolong the expiratory phase (i.e., decreasing the I : E by low respiratory rate, high flows, and short inspiratory time) while tolerating hypercapnia and acidosis [25, 26]. This "lack of practice" may also explain the high level of PEEP selected in a paralyzed patient where no trigger asynchrony could occur and where, although controversial, it could worsen air trapping [27, 28]. Lastly, low tidal volume ventilation is being applied to everyone [29]. Although the trend in patient with status asthmaticus [24] was present prior to the ARDS net seminal article [23] it was likely enhanced by it. As a matter of fact, the tidal volume recommended in review articles through time has decreased (1980's: 10–12 [26, 30] 1990's: 8–10 [26, 31] 2000's: 8–10 [32], 6–8 [28, 33] 5–7 [34, 35] mL/kg) in the absence of any new clinical observations since those of Darioli and Perret [25] and Tuxen et al. [26, 36].

There are limitations to our study. First, the survey sampled critical care physicians and respiratory therapists in a single large academic institution. The poor response rate may have been due to the time of the year (December holidays) and inadequate delivery of the survey (i.e., to some departments the survey was made available through a website rather than direct email). While recognizing that the sample is small and obtained during a holiday period, the objective of the survey was to obtain a measure of how clinicians react to ventilation scenarios. The survey may not represent regional or national practices; however, it represents a snap shot of mechanical ventilation in a large academic institution during a given moment in time. It can be argued that "expert" clinicians would do better than what the survey revealed, or that guidelines indicate different courses of action. We concede that setting the ventilator is a complex process where changes to parameters should be made in response to airway pressure measurements and clinical findings. Further, the initial settings are changed according to response, sometimes immediately. Yet, the survey results do demonstrate that clinicians sometimes fail to follow guidelines, protocols, or physiology. "Expert" clinicians are not available at the bedside all the time. The variability in settings chosen by clinicians, some against common teachings, is the strength of the study. This variablity represents differences in humans experience, levels of education, and propensity to follow protocols. For better or worse, computers assure adherence to protocols.

Another limitation is the reliance on a relatively simple version of the equation of motion as the basis for the mathematical models used by the computer algorithms and the lung simulator. The equation considers the lung as a single alveolar unit with constant compliance and resistance, which is an oversimplification of the heterogeneous nature of the lung, particularly in disease states. However, two factors support its application in this study. First, the equation of motion has been used in commercially available ventilator targeting schemes (Proportional Assist Ventilation Plus, Proportional Pressure Support, and Adaptive Support Ventilation) [9, 37]. Second, and most important to our study, Belliato et al. [8] demonstrated that in passive conditions, the lung simulator we used, when programmed with the measured patient lung resistance and compliance behaved identically to the patients studied (same pressures, and volumes). The simulator allowed us to obtain data which

would have been impossible to obtain in "real life conditions" since the same patients could not be sensibly placed on three ventilator settings without changing the clinical and respiratory system status.

Another limitation is the lack of respiratory effort during this study. The absence of respiratory effort in clinical practice is the exception rather than the rule. For example, Arnal et al. [9] showed that in spontaneously breathing patients, the ventilator settings chosen by ASV were similar regardless of physiology, and were only different in extreme restrictive and obstructive lung disease. ASV uses adaptive pressure targeting in spontaneously breathing patients. That is, the patient decides the tidal volume and respiratory rate, thus the observed breathing pattern is less dependent on the ventilator settings and more dependent on the patient respiratory drive. It is still to be determined what the behavior and role of MFV would be in spontaneously breathing patients.

Finally, the fact that ASV and MFV use a closed loop control to find the settings to achieve the target minute ventilation means that the initial settings chosen by the device are adjusted over the next minutes to achieve the target goal. This would inherently bias the results towards ASV and MFV, as the clinician did not have a chance to optimize its settings based on ventilation outcomes. However, the goal of the study was to demonstrate the differences in choices, and given that this was a static model, the settings chosen by the closed loop algorithms had minimal variation.

6. Conclusions

Computer controlled targeting schemes may result in similar ventilator settings to those chosen by a clinician (e.g., ASV in normal lung physiology) or very different settings (e.g., MFV in ARDS physiology delivering less volume and pressure) for the same minute ventilation goal. The targeting scheme's goal and its interaction with the lung physiological characteristics explain these differences.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgment

No source of funding to report. Portions of this study were presented as an abstract/oral presentation at the CHEST meeting in Philadelphia, USA, in 2008.

References

[1] T. P. Laubscher, A. Frutiger, S. Fanconi, and J. X. Brunner, "The automatic selection of ventilation parameters during the initial phase of mechanical ventilation," *Intensive Care Medicine*, vol. 22, no. 3, pp. 199–207, 1996.

[2] F. Lellouche, J. Mancebo, P. Jolliet et al., "A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation," *American Journal of Respiratory and Critical Care Medicine*, vol. 174, no. 8, pp. 894–900, 2006.

[3] E. Kondili, G. Prinianakis, C. Alexopoulou, E. Vakouti, M. Klimathianaki, and D. Georgopoulos, "Respiratory load compensation during mechanical ventilation—proportional assist ventilation with load-adjustable gain factors versus pressure support," *Intensive Care Medicine*, vol. 32, no. 5, pp. 692–699, 2006.

[4] R. L. Chatburn and E. Mireles-Cabodevila, "Closed-loop control of mechanical ventilation: description and classification of targeting schemes," *Respiratory Care*, vol. 56, no. 1, pp. 85–98, 2011.

[5] R. S. Campbell, R. D. Branson, and J. A. Johannigman, "Adaptive support ventilation," *Respiratory Care Clinics of North America*, vol. 7, no. 3, pp. 425–440, 2001.

[6] F. T. Tehrani, "Automatic control of mechanical ventilation. Part 1: theory and history of the technology," *Journal of Clinical Monitoring and Computing*, vol. 22, no. 6, pp. 409–415, 2008.

[7] D. M. Linton, G. Renov, J. Lafair, L. Vasiliev, and G. Friedman, "Adaptive Support Ventilation as the sole mode of ventilatory support in chronically ventilated patients," *Critical Care and Resuscitation*, vol. 8, no. 1, pp. 11–14, 2006.

[8] M. Belliato, A. Palo, D. Pasero, G. A. Iotti, F. Mojoli, and A. Braschi, "Evaluation of adaptive support ventilation in paralysed patients and in a physical lung model," *International Journal of Artificial Organs*, vol. 27, no. 8, pp. 709–716, 2004.

[9] J. M. Arnal, M. Wysocki, C. Nafati et al., "Automatic selection of breathing pattern using adaptive support ventilation," *Intensive Care Medicine*, vol. 34, no. 1, pp. 75–81, 2008.

[10] E. Mireles-Cabodevila and R. L. Chatburn, "Mid-frequency ventilation: unconventional use of conventional mechanical ventilation as a lung-protection strategy," *Respiratory Care*, vol. 53, no. 12, pp. 1669–1677, 2008.

[11] T. P. Laubscher, A. Frutiger, S. Fanconi, H. Jutzi, and J. X. Brunner, "Automatic selection of tidal volume, respiratory frequency and minute ventilation in intubated ICU patients as startup procedure for closed-loop controlled ventilation," *International Journal of Clinical Monitoring and Computing*, vol. 11, no. 1, pp. 19–30, 1994.

[12] D. Tassaux, E. Dalmas, P. Gratadour, and P. Jolliet, "Patient-ventilator interactions during partial ventilatory support: a preliminary study comparing the effects of adaptive support ventilation with synchronized intermittent mandatory ventilation plus inspiratory pressure support," *Critical Care Medicine*, vol. 30, no. 4, pp. 801–807, 2002.

[13] R. W. Schrier, *Renal and Electrolyte Disorders*, R.W. Schrier 2010, Lipincott Williams & Wilkins, Philadelphia, Pa, USA, 6th edition.

[14] P. Pelosi, M. Croci, I. Ravagnan, P. Vicardi, and L. Gattinoni, "Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients," *Chest*, vol. 109, no. 1, pp. 144–151, 1996.

[15] C. Broseghini, R. Brandolese, R. Poggi et al., "Respiratory mechanics during the first day of mechanical ventilation in patients with pulmonary edema and chronic airway obstruction," *American Review of Respiratory Disease*, vol. 138, no. 2, pp. 355–361, 1988.

[16] K. P. Steinberg, L. D. Hudson, R. B. Goodman et al., "Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome," *The New England Journal of Medicine*, vol. 354, no. 16, pp. 1671–1684, 2006.

[17] M. I. Gold and M. Helrich, "Pulmonary mechanics during general anesthesia: V. Status asthmaticus," *Anesthesiology*, vol. 32, no. 5, pp. 422–428, 1970.

[18] R. L. Chatburn, "Classification of ventilator modes: update and proposal for implementation," *Respiratory Care*, vol. 52, no. 3, pp. 301–323, 2007.

[19] P. C. Gruber, C. D. Gomersall, P. Leung et al., "Randomized controlled trial comparing adaptive-support ventilation with pressure-regulated volume-controlled ventilation with automode in weaning patients after cardiac surgery," *Anesthesiology*, vol. 109, no. 1, pp. 81–87, 2008.

[20] C. F. Sulzer, R. Chioléro, P. G. Chassot, X. M. Mueller, and J. P. Revelly, "Adaptive support ventilation for fast tracheal extubation after cardiac surgery: a randomized controlled study," *Anesthesiology*, vol. 95, no. 6, pp. 1339–1345, 2001.

[21] A. H. Petter, R. L. Chioléro, T. Cassina, P. G. Chassot, X. M. Müller, and J. P. Revelly, "Automatic "Respirator/Weaning" with adaptive support ventilation: the effect on duration of endotracheal intubation and patient management," *Anesthesia and Analgesia*, vol. 97, no. 6, pp. 1743–1750, 2003.

[22] V. R. Ramnath, D. R. Hess, and B. T. Thompson, "Conventional mechanical ventilation in acute lung injury and acute respiratory distress syndrome," *Clinics in Chest Medicine*, vol. 27, no. 4, pp. 601–613, 2006.

[23] "Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome," *The New England Journal of Medicine*, vol. 342, no. 18, pp. 1301–1308, 2000.

[24] C. C. Kao, S. Jain, K. K. Guntupalli, and V. Bandi, "Mechanical ventilation for asthma: a 10-year experience," *Journal of Asthma*, vol. 45, no. 7, pp. 552–556, 2008.

[25] R. Darioli and C. Perret, "Mechanical controlled hypoventilation in status asthmaticus," *American Review of Respiratory Disease*, vol. 129, no. 3, pp. 385–387, 1984.

[26] D. V. Tuxen and S. Lane, "The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction," *American Review of Respiratory Disease*, vol. 136, no. 4, pp. 872–879, 1987.

[27] M. P. Caramez, J. B. Borges, M. R. Tucci et al., "Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation," *Critical Care Medicine*, vol. 33, no. 7, pp. 1519–1528, 2005.

[28] B. D. Medoff, "Invasive and noninvasive ventilation in patients with asthma," *Respiratory Care*, vol. 53, no. 6, pp. 740–748, 2008.

[29] O. Gajic, S. I. Dara, J. L. Mendez et al., "Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation," *Critical Care Medicine*, vol. 32, no. 9, pp. 1817–1824, 2004.

[30] P. K. Franklin, "Review of acute severe asthma," *Western Journal of Medicine*, vol. 150, no. 5, pp. 552–556, 1989.

[31] B. D. Levy, B. Kitch, and C. H. Fanta, "Medical and ventilatory management of status asthmaticus," *Intensive Care Medicine*, vol. 24, no. 2, pp. 105–117, 1998.

[32] M. Oddo, F. Feihl, M. D. Schaller, and C. Perret, "Management of mechanical ventilation in acute severe asthma: practical aspects," *Intensive Care Medicine*, vol. 32, no. 4, pp. 501–510, 2006.

[33] D. R. Stather and T. E. Stewart, "Clinical review: mechanical ventilation in severe asthma," *Critical Care*, vol. 9, no. 6, pp. 581–587, 2005.

[34] C. S. Barbas, V. Pinheiro Bdo, A. Vianna et al., "Mechanical ventilation in acute asthma crisis," *Jornal Brasileiro de Pneumologia*, vol. 33, supplement 2, pp. S106–S110, 2007.

[35] P. Phipps and C. S. Garrard, "The pulmonary physician in critical care• 12: acute severe asthma in the intensive care unit," *Thorax*, vol. 58, no. 1, pp. 81–88, 2003.

[36] D. V. Tuxen, T. J. Williams, C. D. Scheinkestel, D. Czarny, and G. Bowes, "Use of a measurement of pulmonary hyperinflation to control the level of mechanical ventilation in patients with acute severe asthma," *American Review of Respiratory Disease*, vol. 146, no. 5, pp. 1136–1142, 1992.

[37] M. Younes, "Proportional assist ventilation, a new approach to ventilatory support: theory," *American Review of Respiratory Disease*, vol. 145, no. 1, pp. 114–120, 1992.

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 606179, 11 pages
doi:10.1155/2012/606179

Research Article

Characteristics of Hemodynamic Disorders in Patients with Severe Traumatic Brain Injury

Ryta E. Rzheutskaya

Department of Anesthesiology and Intensive Care, Belarusian State Medical University, Dzerzhinsky Avenue 83, 220116 Minsk, Belarus

Correspondence should be addressed to Ryta E. Rzheutskaya, rgeutskaja@mail.ru

Received 29 May 2012; Revised 31 July 2012; Accepted 11 August 2012

Academic Editor: Mikhail Y. Kirov

Purpose. To define specific features of central hemodynamic parameter changes in patients with isolated severe traumatic brain injury (STBI) and in patients with clinically established brain death and to determine the required course of treatment for their correction. *Data and Research Methods*. A close study of central hemodynamic parameters was undertaken. The study involved 13 patients with isolated STBI (group STBI) and 15 patients with isolated STBI and clinically established brain death (group STBI-BD). The parameters of central hemodynamics were researched applying transpulmonary thermodilution. *Results*. In the present study, various types of hemodynamic reaction (normodynamic, hyperdynamic, and hypodynamic) were identified in patients with isolated STBI in an acute period of traumatic disease. Hyperdynamic type of blood circulation was not observed in patients with isolated STBI and clinically established brain death. Detected hemodynamic disorders led to the correction of the ongoing therapy under the control of central hemodynamic parameters. *Conclusions*. Monitoring of parameters of central hemodynamics allows to detect the cause of disorders, to timely carry out the required correction, and to coordinate infusion, inotropic, and vasopressor therapy.

1. Introduction

Pathophysiological changes arising after primary brain injury lead to the secondary brain injury [1–3]. Both prehospital and inhospital hypotensions have been shown to have a deleterious influence on outcome from severe traumatic brain injury (STBI) [2, 4–6]. The development of hypotension in patients with STBI can be caused by the reduction of systematic vascular resistance as a result of injury of diencephalic region, the increase of cerebral dislocation signs, and the development of adrenal insufficiency. Another reason for hypotension can be a drop of cardiac output due to the reduction of contractility or hypovolemia, which develops as a result of fluid loss during bleeding, dehydration therapy, diabetes insipidus, and hyperthermia. Hypovolemia initiates the centralization of blood circulation which subsequently brings a number of adverse effects, such as stasis and sludge of erythrocytes in capillaries, ischemia of organs and tissues, tissue edema, and multiple organ failure. Neurogenic Stunned Myocardium (NSM) is still another reason for hypotension, but it has rarely been reported in association with STBI [7]. The main purpose of the ongoing therapy is to prevent and correct hypotension (systolic blood pressure (SBP) < 90 mmHg) [4, 8, 9] and to maintain the target figures of cerebral perfusion pressure (CPP) in the range of 50–70 mmHg [8, 10, 11].

Traumatic brain injury is one of the main causes of brain death in the intensive care units. One of the key problems that arise in the majority of donors with brain damage is acute cardiovascular insufficiency, where hypovolemia plays a special role [12]. The more evident hypovolemia is, the higher the concentration of interleukin-6 and the lower the survival rate of transplant are [13, 14]. One more reason for hypotension may be myocardial dysfunction which is observed in 40% of brain death cases [15, 16].

A clear pathophysiological conception of hemodynamic disorders in patients with STBI and in patients with established brain death is an important premise for the rational plan of infusion and inotropic/vasopressor therapy.

The purpose of the present research was to define specific features of central hemodynamic parameter changes in patients with isolated severe traumatic brain injury and in patients with isolated severe traumatic brain injury and clinically established brain death and to determine the required course of treatment for their correction.

2. Materials and Methods

Meeting the goals of the National Vietnamese Scientific Research: Providing Kidney and Liver Transplantation from Brain-Dead Donors Program, a close study of central hemodynamic parameters was undertaken at the Intensive Therapy Division of Viet Duc University Hospital (Hanoi, Vietnam) from October 2009 until June 2010.

The study involved 13 patients with isolated STBI (group STBI) and 15 patients with isolated STBI and clinically established brain death (group STBI-BD). The level of consciousness was assessed using Glasgow Coma Scale Score (GCS).

Inclusion criteria for group STBI were (1) isolated STBI; (2) GCS 4–7 points on admission to the intensive care unit (ICU); (3) age 18 and older; (4) acute period of STBI (not later than 48 h from the moment of getting trauma. Patients were not always brought to the ICU right after the operation; they could have been held in the emergency recovery room for a period lasting from several hours to 2 days, lacking necessary facilities for central hemodynamic monitoring); (5) absence of concomitant diseases.

Inclusion criteria for group STBI-BD were (1) isolated STBI as a reason of brain death; (2) GCS 3 points; (3) age 18 and older; (4) established brain death (clinical observation, proved using EEG, cerebral angiography); (5) absence of concomitant diseases. The main reasons for STBI were road traffic accidents (a motorbike accident) and falls from height.

The parameters of central hemodynamics were researched applying PiCCO technology using PiCCO2 monitor produced by PULSION Medical Systems (Germany), as well as Philips IntelliVue MP30 patient monitor with the hemo-dynamic PiCCO-Technology Module M3012A#C10 produced by Philips Medical Systems. All patients had a central venous catheter inserted in the subclavian vein and a 4F 16 cm femoral arterial catheter used for transpulmonary thermodilution (PulsioCath PV2014L16; Pulsion Medical Systems, Munich, Germany). PiCCO technology is based on a combination of two methods: transpulmonary thermodilution and arterial pulse contour analysis [17]. The combination provides continuous measurement of myocardial contractility and volumetric preload, control of afterload, monitoring of cardiac response to volume loading, and interstitial fluid balance in the lungs [18–20]. Triplicate central venous injections of 15 mL ice-cold saline (<8°C) were performed. The module showed the following parameters: mean arterial blood pressure (MAP, mmHg), cardiac index (CI, normal value 3.0–5.0 L/min/m^2), stroke volume index (SVI, normal value 40–60 mL/m^2), systemic vascular resistance index (SVRI, normal value 1200–2000 dyn$*$s$*$cm$^{-5}*$m^2), global end-diastolic volume index (GEDI, normal value 680–800 mL/m^2), stroke volume variation (SVV, normal value $\leq$ 10%), global ejection fraction (GEF, normal value 25–35%), cardiac function index (CFI, normal value 4.5–6.5 l/min). As an additional parameter extravascular lung water index (ELWI, normal value 3.0–7.0 mL/kg) was also determined. ELWI allows to detect the content of fluid in the pulmonary interstitium. In case of increasing ELWI the type of edema can be defined using pulmonary vascular permeability index (PVPI, normal value 1.0–3.0) [21]. The number of thermodilution measurements for the calibration of continuous CI measurement was from 3 to 7 times a day, subject to the condition of hemodynamics. central venous pressure (CVP, normal value 2–10 mmHg) was monitored before each thermodilution measurement.

Group STBI patients were monitored in an acute period of traumatic disease from the first day in the ICU for 7 days in the light of the ongoing therapy (infusion therapy, vasopressor support). Group STBI-BD patients' central hemodynamic parameters were monitored for 1–3 days from the onset of brain death establishment in the light of the ongoing therapy.

Intracranial pressure monitoring was provided using "Integra NeuroSciences Camino MPM1" monitor in 4 patients of group STBI. It was performed simultaneously with the central hemodynamic parameters monitoring. A Camino catheter was placed into the parenchyma. The monitoring of the intracranial pressure (ICP) was conducted in real time. The cerebral perfusion pressure (CPP) was calculated according to the following formula: CPP = MAP − ICP.

The statistical processing of the data was carried out using specialized software (MS Excel, Statistica 6.0, Biostatistics for Windows, version 4.03). Student's t-test was used to estimate the significance of intergroup differences. Single factor analysis of variance followed by Student's t-test with Bonferroni correction was used to estimate the significance of intragroup differences. The results are presented in the following format: $M \pm \sigma$ (mean ± standard deviation). Spearman's Rank Correlation Method was used to assess the degree of correlation between parameters. A P value of 0.05 or less was considered statistically significant.

3. Results

The demographic and clinical characteristics of the patients of group STBI are presented in Table 1. The brain CT scan revealed compression of the brain by acute intracranial hematomas (epidural and subdural), associated with severe contusion in 11 (84.6%) patients. They required a surgery. 2 patients had severe brain contusion with accompanying traumatic subarachnoid hemorrhage (SAH). They were not operated. The condition of the patients was assessed critical. The patients entered the ICU either right after operation, or after staying in the emergency recovery room. The patients who did not need the operation entered the ICU right away. 7 patients (53.8%) required hemotransfusion on the first day. Dehydration therapy using Mannitol 20% (0.25–1 g/kg) was given by indication (according to clinical signs of intracranial hypertension or results of monitoring of ICP). In condition

Table 1: Characteristics of patients with STBI (group STBI).

Patients (variants)	Gender, age (years)	GCS, points	Operation	Hemotransfusion	Use of Mannitol	CVP, mmHg	Norepinephrine μg/kg/min	Adrenaline μg/kg/min	Rate of infusion mL/kg/day	Urine output mL/kg/h	Length of stay in the ICU	Outcome
1 (STBI-a)	M, 46	6	+	+	+	5	0.12	—	114	1.6	20	Favorable
2 (STBI-a)	M, 20	6	+	+	+	10	—	—	135	2.8	8	Favorable
3 (STBI-a)	M, 21	7	+	+	−	4	—	—	82	1.5	11	Favorable
4 (STBI-a)	F, 43	6	+	+	−	10	0.27	0.17	116	8.6	3	Death
5 (STBI-b)	M, 39	5	−	−	+	4	0.1	—	48	1.4	37	Favorable
6 (STBI-b)	M, 25	4	+	−	+	5	0.13	—	122	2.9	12	Favorable
7 (STBI-b)	M, 45	6	−	−	+	5	0.12	—	49	3.0	19	Favorable
8 (STBI-c)	M, 60	5	+	−	−	6	0.2	—	50	2.4	14	Death
9 (STBI-c)	M, 49	6	+	+	+	2	0.12	—	35	1.2	21	Favorable
10 (STBI-c)	M, 38	4	+	+	−	10	—	—	54	2.1	13	Favorable
11 (STBI-c)	M, 29	6	+	−	−	5	—	—	47	1.9	9	Favorable
12 (STBI-d)	M, 20	6	+	+	−	10	0.13	—	100	2.8	8	Favorable
13 (STBI-d)	M, 72	6	+	+	−	9	—	—	36	1.5	21	Favorable

GCS, CVP, use of mannitol, doses of norepinephrine and adrenaline are presented at the moment of the monitoring beginning, rate of infusion, urine output, use of mannitol on the first day of the monitoring,
M: male, F: female.

of sedation (fentanyl 0.6–0.9 μg/kg/h and midazolam 0.025–0.035 mg/kg/h) pressure control mechanical ventilation was carried out to all patients. All patients received antibacterial therapy and infusion therapy: on the first day isotonic crystalloid and colloid solutions were infused at the average rate of 98.2 ± 43 mL/kg/day. To reach the target value of SBP higher than 90 mmHg and to maintain the value of CPP within the range of 50–70 mmHg, in 8 patients (62%) vasopressor support with norepinephrine infusions at the average rate of 0.12 ± 0.04 μg/kg/min was used prior to the monitoring of the parameters of central hemodynamics (Table 1).

Based on the assessment of central hemodynamic parameters obtained on the first day, 4 variants were detected depending on the type of hemodynamic response in patients of group STBI (Figure 1).

Variant STBI-a patients (4 (30.8%) patients) had a hypodynamic type of blood circulation (CI 2.68 ± 0.48 L/min/m^2) with a high systemic vascular resistance. They had apparent hypovolemia with significant decrease in preload—GEDI ranged from 247 to 473 mL/m^2 (mean, 353 ± 71.7 mL/m^2). Their SVI decreased to 30.2 ± 5.1 mL/m^2. SVV, which assesses cardiac responsiveness to volume loading, exceeded its normal value of less than or equal to 10% and reached 18.5 ± 3%. No apparent tachycardia was observed (HR 91.9 ± 9 beats/min). MAP amounted to 95.8 ± 6 mmHg. Hemodynamic measurements taken after volume loading with Voluven (6% hydroxyethyl starch) 500 mL showed a significant rise of SVI by 10% ($P < 0.05$) in patient no. 4. Moreover, SVI increased by more than 15% in comparison to the initial index in other 3 patients (75%) of this hemodynamic variant. There was an increase of CI, GEDI, GEF, CFI, and decrease of SVV ($P < 0.05$). So, the infusion therapy using crystalloids and colloids (at the average rate of 110 mL/kg/day) was extended. The doses of norepinephrine under SVRI monitoring were reduced to 0.02 μg/kg/min in patient no. 1 and to 0.2 μg/kg/min in patient no. 4. As the result of the ongoing therapy in patients no. 1, 2, 3 by the end of the 1st day of the treatment held under the control of the central hemodynamic parameters monitoring the hypodynamic type of blood circulation with a high systemic vascular resistance changed into the normodynamic one with normal systemic vascular resistance (Figure 3). The condition was preserved on the following day. In patient No. 1 titration of norepinephrine under SVRI monitoring at 0.02 μg/kg/min was run for three days and got cancelled afterwards. In patient No. 2 by the end of the 2nd day a decline of CI with bradycardia and some drop of SVRI were detected. As a result, titration of adrenaline at 0.1 μg/kg/min was used for 5 days. In patient No. 3 at the end of the 2nd day normodynamic type of blood circulation with normal systemic vascular resistance transformed into hyperdynamic type of blood circulation with a low systemic vascular resistance. In the run of the norepinephrine titration at 0.13 μg/kg/min lasting for several hours, SVRI and CI were normalized. The dose of norepinephrine was reduced to 0.1 μg/kg/min on the 3rd day, after which it was cancelled. Starting from the 2nd day the infusion volume reached on average 40 mL/kg/day in these three patients.

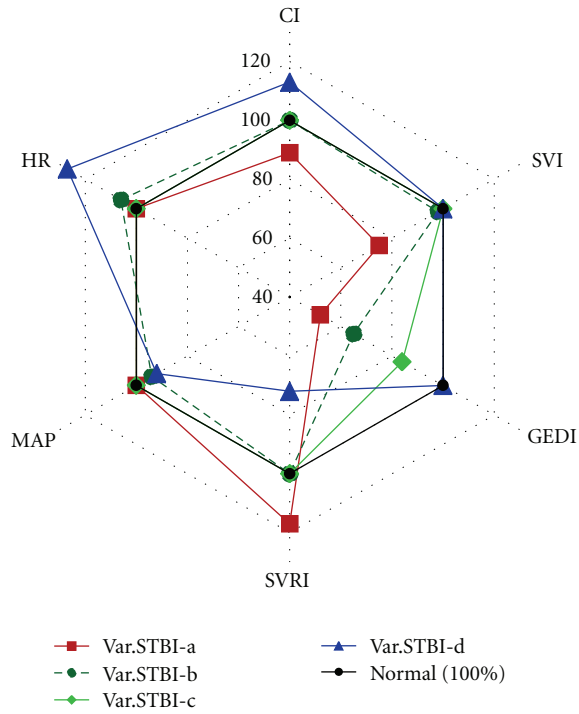


Figure 1: Variants of hemodynamic reaction in the patients of group STBI on the first day. Note. Hemodynamic parameters are presented with percents from the normal value.

Patient No. 4 had hypotension from the moment of entering the hospital and received a combination of adrenaline at 0.17 μg/kg/min and norepinephrine at 0.27 μg/kg/min (Table 1) combined with the ongoing infusion therapy. By the end of the 1st day of trauma, diabetes insipidus developed. Central hemodynamics parameter monitoring, started at the beginning of the 2nd day of trauma, revealed the above-mentioned type of hemodynamics characterized by apparent hypovolemia with significant decrease in preload (the lowest GEDI 247 mL/m^2). Despite the extension of volume loading and the decrease in the dose of norepinephrine, hypodynamic type of blood circulation with a high systemic vascular resistance was preserved in the patient (Figure 4). On the 2nd day of the monitoring, at the background of hypodynamic type of blood circulation a sharp decline of SVRI was registered in spite of the increase in the dosage of adrenaline and norepinephrine, leading to the subsequent circulatory arrest.

Variant STBI-b patients (3 (23.1%) patients) had normodynamic type of blood circulation (CI 3.7 ± 0.8 L/min/m^2) with normal systemic vascular resistance. Some decrease in preload—GEDI ranged from 368 to 587 mL/m^2 (mean, 494 ± 56.6 mL/m^2)—and a slight decrease of SVI to the level of 39.3 ± 6.86 mL/m^2 were observed. SVV exceeded its normal value (20.3 ± 9.2%). No apparent tachycardia was observed (HR 95.6 ± 20.1 beats/min). MAP amounted to 84.8 ± 8.8 mmHg. Hemodynamic measurements taken after a volume loading with Voluven 500 mL showed a significant rise of SVI by 11–27% ($P < 0.05$). In 2 (67%) out of 3 patients

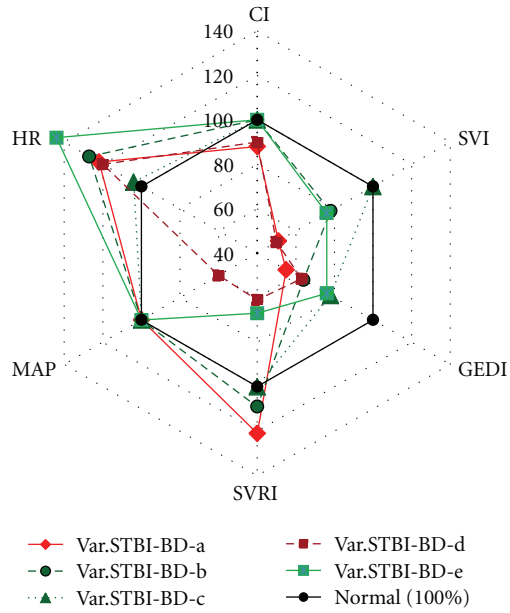


Figure 2: Variants of hemodynamic reaction in the patients of group STBI-BD on the first day. Note. Hemodynamic parameters are presented with percents from the normal value.

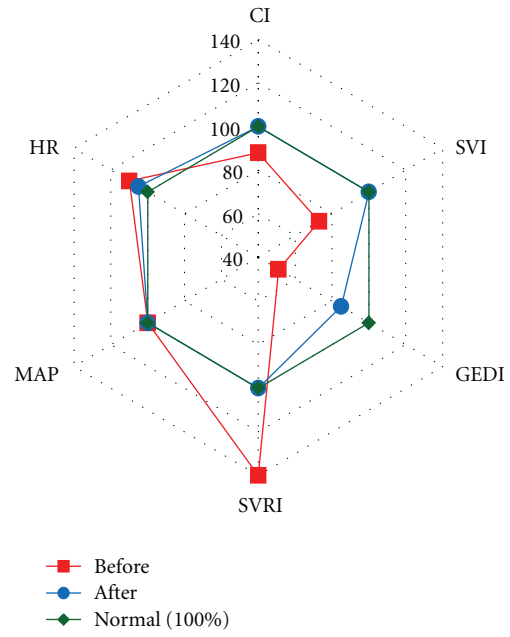


Figure 3: Variant STBI-a of hemodynamic reaction on the first day of monitoring before and after correction. Note. Hemodynamic parameters are presented with percents from the normal value.

SVI increased by more than 15% from the initial value. An increase of CI, GEDI, GEF, CFI and decrease of SVV ($P < 0.05$) were detected. On the first day, under the control of hemodynamic monitoring and in accordance with the response to volume loading, isotonic crystalloid and colloid solutions were infused at the average rate of 70 mL/kg/day. During the 1st day of the monitoring hypovolemia was

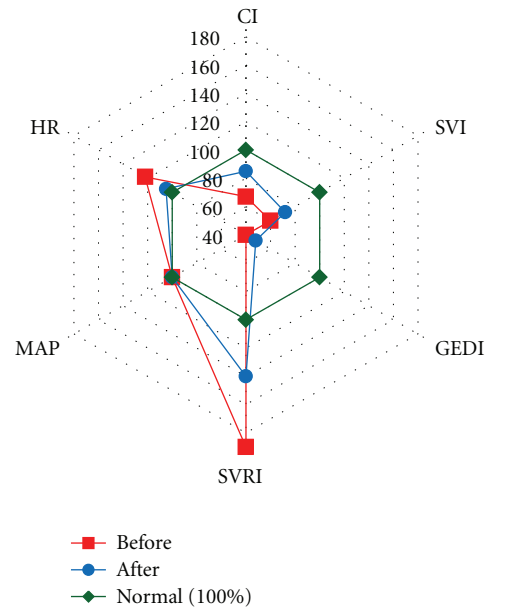


Figure 4: Variant STBI-a of hemodynamic reaction—patient no. 4 on the first day of monitoring before and after correction. Note. Hemodynamic parameters are presented with percents from the normal value.

corrected in all patients (Figure 5). Starting the 2nd day, the infusion volume in these patients was given with an average rate of 35–40 mL/kg/day.

Patient No. 5 was provided with invasive monitoring of ICP. In the run of the monitoring, intracranial hypertension was registered. Therefore, the patient was receiving mannitol from day 1 to day 7. All patients of variant STBI-b received norepinephrine for 10–15 days starting from the first day. On the 4th day, a decline of SVRI was detected in patient No. 7. It called for the increase of the doses of norepinephrine.

Variant STBI-c patients (4 (30.8%) patients) had normodynamic type of blood circulation (CI 4.08 ± 0.6 L/min/m^2), with normal SVRI. GEDI rose from 378 to 795 mL/m^2 (mean, 573 ± 85 mL/m^2). SVI and SVV were within normal values. No tachycardia was observed (HR 77.2 ± 10.4 beats/min). MAP increased to 90.5 ± 11.2 mmHg. Hemodynamic measurements taken after volume loading with Voluven 500 mL showed a significant rise of SVI, by 11–27% ($P < 0.05$). SVI increased by more than 15% in comparison to the initial index in 3 (75%) of a total of 4 patients. An increase of CI, GEDI, GEF, and CFI ($P < 0.05$) was detected. On the first day, under the control of hemodynamic monitoring in accordance with the response to volume loading isotonic crystalloid and colloid solutions were infused at the average rate of 50 mL/kg/day. During the 1st day of the monitoring hypovolemia was eliminated in all patients. Starting the 2nd day, the infusion volume in these patients was given with an average rate of 30–35 mL/kg/day.

To patients No. 8 and No. 9 invasive monitoring of ICP was provided. In patient No. 9 intracranial hypertension was registered, so the patient received mannitol on the 4th and the 5th days. Patient No. 10 received norepinephrine only

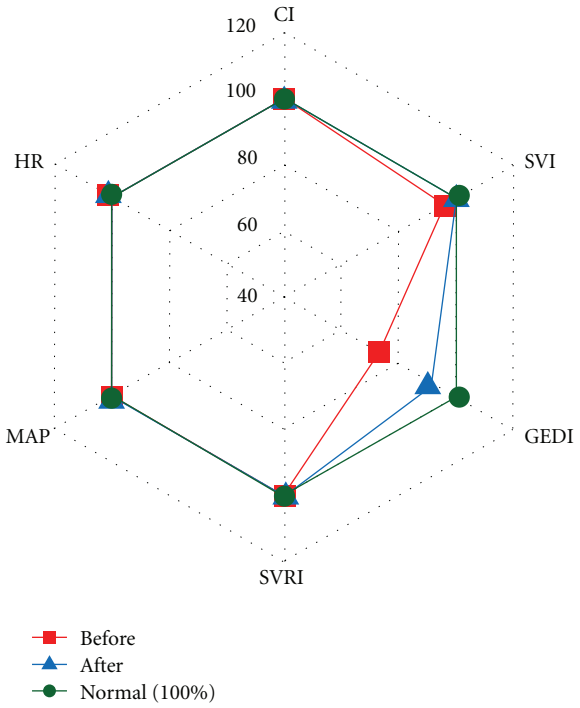


Figure 5: Variant STBI-b of hemodynamic reaction before (the first measment) and after correction in the patients of group STBI on the first day. Note. Hemodynamic parameters are presented with percents from the normal value.

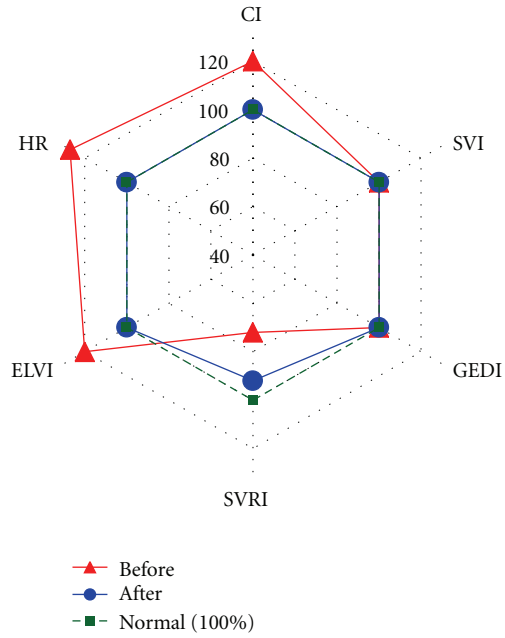


Figure 6: Hyperdynamic type of blood circulation in the patients of group STBI on the first day before and after correction. Note. Hemodynamic parameters are presented with percents from the normal value.

during the operation. On the 4th day, a decline of SVRI was detected in patient No. 9. That required an increase of the norepinephrine doses, lasting for 14 days. Patient No. 11 did not need any norepinephrine. Patient No. 8 received norepinephrine starting from the first day. On the 3rd day in order to normalize SVRI the dose was increased. Moreover, on the 8th day a combination of adrenaline at 0.12 μg/kg/min was used.

Variant STBI-d patients ((15.4%) 2 patients) had a hyperdynamic type of blood circulation (CI 5.65 ± 0.8 L/min/m^2) with a low systemic vascular resistance. They had normovolemia with GEDI 705.1 ± 84.5 mL/m^2 (GEDI amounted from 584 to 880 mL/m^2). SVI and SVV were within normal values. Tachycardia (HR 115 ± 18 beats/min) was observed. MAP amounted to 83.1 ± 2.4 mmHg. Hemodynamic measurements taken after a volume loading with Voluven 500 mL showed a significant rise of SVI by 18% in comparison with the initial index in patient No. 12. An increase of CI, GEDI, GEF, and CFI ($P < 0.05$) was detected. On the first day, under the control of hemodynamic monitoring in accordance with the response to volume loading isotonic crystalloid and colloid solutions were infused at the average a rate of 35 mL/kg/day.

Taking into consideration the low level of SVRI along with norepinephrine usage by patient No. 12, his dose was raised to 0.17 μg/kg/min and the titration was kept on for the following 7 days. For the correction of the low SVRI in patient No. 13 the titration of norepinephrine at the dose of 0.07 μg/kg/min was started and lasted for the following three days.

ELWI rose in both patients of group 4 without changes in arterial blood gas analyses and in roentgenologic results and reached 10 ± 1.8 mL/kg. It required infusion load limitation and the stimulation of diuresis (lasix) that allowed to normalize ELVI. As a result of the ongoing therapy by the end of the 1st day of monitoring the normodynamic type of blood circulation with normal SVRI was registered in the patients (Figure 6).

To patient No. 13 invasive monitoring of ICP was provided. Intracranial hypertension was registered, so the patient received mannitol on the 4th and 5th days.

The demographic and clinical characteristics of the patients of group STBI-BD are presented in Table 2. 9 (60%) patients suffered from compression of the brain by acute intracranial hematomas (epidural and subdural), associated with severe contusion. 8 (53.3%) patients required surgery before the brain death establishment. 3 patients had severe brain contusion. 3 patients had severe brain contusion with accompanying traumatic SAH. Infusion therapy: isotonic crystalloid and colloid solutions were infused at the average rate of 69.3 ± 16 mL/kg/day on the first day of brain death establishment. 8 patients (53.3%) required hemotransfusion on the first day. To reach the target of MAP higher than 70 mmHg vasopressor support was carried out in all patients. In 9 (60%) patients hypernatremia was observed, and in 11 patients (73.3%) diabetes insipidus was detected (Table 2).

Based on the assessment of central hemodynamic parameters obtained on the first day, 5 variants depending on

Table 2: Characteristics of patients with STBI and clinically established brain death (group STBI-BD).

Patients (variants)	Gender age (years)	Operation	Hemotransfusion	Diabetes insipidus	CVP, mmHg	Norepinephrine μg/kg/min	Adrenaline μg/kg/min	Rate of infusion mL/kg/day	Urine output mL/kg/h	Use of minirin	Day from trauma
1 (STBI-BD-a)	M, 21	+	+	+	9	0.15	—	54	3.9	−	6
2 (STBI-BD-a)	M, 21	+	−	+	10	0.3	0.1	155	13.8	+	2
3 (STBI-BD a)	M, 38	−	−	+	4	0.4	0.2	94	8.5	+	1
4 (STBI-BD-a)	M, 34	+	−	+	9	0.19	—	62	5.5	+	5
5 (STBI-BD-a)	M, 26	+	+	−	8	0.15	—	75	2.0	−	3
6 (STBI-BD-a)	M, 55	+	+	+	10	0.6	0.19	84	6.25	+	4
7 (STBI-BD-b)	F, 36	−	+	+	7	0.3	0.15	87	4.0	+	2
8 (STBI-BD-b)	M, 38	−	−	+	3	0.3	—	82	3.1	+	3
9 (STBI-BD-b)	M, 26	−	−	+	6	0.16	—	87	9.6	+	2
10 (STBI-BD-b)	M, 18	−	−	+	4	0.15	—	96	4.9	+	4
11 (STBI-BD-b)	F, 24	+	−	−	6	—	0.15	55	2.95	−	6
12 (STBI-BD-c)	M, 53	+	+	+	9	0.19	—	54	2.62	+	9
13 (STBI-BD-c)	M, 25	−	+	−	4	0.22	—	45	1.4	−	4
14 (STBI-BD-d)	M, 64	−	−	−	12	0.28	0.22	58	0.2	−	1
15 (STBI-BD-e)	M, 44	+	+	+	5	0.4	—	84	4.86	+	3

Day from getting trauma, CVP, use of Minirin, doses of norepinephrine and adrenaline are presented at the moment of the monitoring beginning,
rate of infusion, urine Output, on the first day of the monitoring,
M: male, F: female.

the type of hemodynamic response were detected in patients of group STBI-BD (Figure 2).

Variant STBI-BD-a patients (6 (40%) patients) had a hypodynamic type of blood circulation (CI 2.65 ± 0.36 L/min/m^2) with a high systemic vascular resistance. They had apparent hypovolemia with significant decrease in preload—GEDI ranged from 270 to 615 mL/m^2 (mean, 373.6 ± 81.9 mL/m^2). Their SVI decreased to 20.5 ± 8.51 mL/m^2. SVV, which assesses cardiac responsiveness to volume loading, significantly exceeded its normal value of less or equal to 10% and reached 22.85 ± 8.1%. Tachycardia (HR 110 ± 11.4 beats/min) was observed. MAP amounted to 89.6 ± 20.7 mmHg. Hemodynamic measurements taken after volume loading with 500 mL Voluven showed a significant rise of SVI by less than 15% in comparison with its initial index, and SVI ranged from 20 to 43% ($P > 0.05$) in all patients. An increase of CI, GEDI, GEF, CFI and decrease of SVV ($P < 0.05$) were detected.

In patients No. 1 and 5 at the end of the 1st day of monitoring in the light of the ongoing infusion therapy, the dose of norepinephrine was reduced. Hypodynamic type of blood circulation with a high systemic vascular resistance transformed into a normodynamic type of blood circulation with normal systemic vascular resistance, but on the 2nd day hypodynamic type of blood circulation with a low systemic vascular resistance was registered which required the increase of the doses of vasopressors. In spite of the ongoing therapy, in patients No. 2, 3, 4, 6 (Table 2) hypodynamic type of blood circulation was preserved which apparently was connected with polyuria, badly corrected with minirin and disturbed vascular tone central regulation.

Variant STBI-BD-b patients (5 (33.3 %) patients) had a normodynamic type of blood circulation (CI 3.4 ± 0.4 L/min/m^2) with high systemic vascular resistance. Some decrease in preload—GEDI from 270 to 736 mL/m^2 (mean, 433.6 ± 76.5 mL/m^2)—and a decrease of SVI to the level of 31.4 ± 5 mL/m^2 were observed. SVV exceeded its normal value (19 ± 8.3%). Tachycardia (HR 114.8 ± 12.5 beats/min) was observed. MAP amounted to 93.44 ± 12.7 mmHg. Hemodynamic measurements taken after a volume loading with 500 mL Voluven showed a significant rise of SVI by less than 15% in comparison with its initial index, ($P < 0.05$) in 4 (80%) patients of 5 patients. There was an increase of CI, GEDI, GEF, CFI and decrease of SVV ($P < 0.05$). In patients No. 8 and 9 in the light of the ongoing therapy (Table 2) normodynamic type of blood circulation with high systemic vascular resistance was preserved. In patients No. 7, 10, 11 on the 2nd day of the monitoring hypodynamic type of blood circulation with a high systemic vascular resistance in light of increase of vasopressors doses was registered.

Variant STBI-BD-c patients (2 (13.3%) patients) had a normodynamic type of blood circulation (CI 4.07 ± 0.6 L/min/m^2) with normal systemic vascular resistance. GEDI decreased and reached the level of 530 ± 68.5 mL/m^2 (ranged from 404 to 652 mL/m^2). SVI (44.25 ± 4.8 mL/m^2) and SVV (9.75 ± 3%) were within normal values. No apparent tachycardia was observed (HR 93.9 ± 8.2 beats/min). MAP amounted to 95.3 ± 15.9 mmHg. In patient No. 13 at the background of the ongoing therapy (Table 2) and decreased norepinephrine doses normodynamic type of blood circulation with normal systemic vascular resistance was preserved during the following days. In patient No. 12 on the 2nd day of the monitoring hypodynamic type of blood circulation with a normal systemic vascular resistance was registered at the background of the titration of norepinephrine.

Variant STBI-BD-d patients (1 (6.67%) patient) had hypodynamic type of blood circulation (CI 2.7 ± 0.2 L/min/m^2) with low systemic vascular resistance despite high doses of vasopressors. He had apparent hypovolemia with GEDI 427 mL/m^2. His SVI was very low. Tachycardia (HR 108.5 ± 2 beats/min) was observed. This type of blood circulation was registered 30 minutes before the development of circulation arrest.

Variant STBI-BD-e patients (1 (6.67%) patient) had normodynamic type of blood circulation (CI 3.95 ± 0.8 L/min/m^2) with low systemic vascular resistance. GEDI decreased to 513.3 ± 26.7 mL/m^2. SVI was low (30.5 ± 1.7 mL/m^2). Apparent tachycardia (HR 130 ± 14 beats/min) was observed. MAP amounted to 90.3 ± 12.7 mmHg. Despite the increase in the dose of norepinephrine low SVRI was preserved. Hemodynamic measurements taken in patients with variants STBI-BD-c, STBI-BD-d, STBI-BD-e after a volume loading with Voluven 500 mL did not show any significant rise of SVI in comparison to its initial value.

4. Discussion

So, in 31% of patients of group STBI and in 47% of patients of group STBI-BD the hypodynamic type of blood circulation was detected, and a significant hypovolemia was highlighted (GEDI amounted to 52–55% from the norm, SVV was increased by more than 10%) that led to the drop of SVI (compounded 51–75% from the normal value) and also to the drop of cardiac output. Global ejection fraction (GEF) that characterizes a contractile myocardium function was within normal values in all patients of group STBI and STBI-BD that indicated the absence of cardiac failure.

Apparently the development of hypodynamic type of blood circulation points at the failure of compensatory mechanisms of the blood circulation. It may develop as a result of an absolute hypovolemia which is associated with a significant loss of circulatory blood volume (bleeding, dehydratation therapy, diabetes insipidus, hyperthermia), and also due to a reliable hypovolemia which is associated with the increase of volume of bloodstream as a result of SVR decrease which was due to the disturbed vascular tone central regulation. If the development of hypodynamic type of blood circulation is mainly connected with the loss of circulatory blood volume, its compensation leads to the change of this type of blood circulation into normodynamic one. If there is a combination of an absolute and relative hypovolemia the implementation of vasopressors with infusion therapy is required. If it is impossible to transform the hypodynamic type of blood circulation into the normodynamic one for several hours, it points at a significant (irreversible) damage of central vasoconstrictive mechanisms. It was not possible to manage the transformation of the hypodynamic type of

blood circulation into the normodynamic type in one (lethal outcome) of 4 patients of group STBI and in 4 patients of 6 patients of group STBI-BD. So, the hypodynamic type of blood circulation is unfavourable in a prognostic way. These findings are consistent with other studies [22, 23] demonstrating that survivors after trauma had higher CI than nonsurvivors. Patients with head injuries who subsequently became brain dead initially had low CI with poor tissue perfusion beginning shortly after emergency department admission [24].

Normodynamic type of blood circulation was observed in 54% of patients of group STBI and in 53% of patients of group STBI-BD who suffered from hypovolemia (GEDI amounted to 64–84% from normal value) which is less expressed in comparison with the patients with hypodynamic type of blood circulation. SVI was normal or slightly decreased. Normal cardiac output was provided by tachycardia with decreased SVI. For the correction of absolute hypovolemia in patients with the hypodynamic type of blood circulation a larger volume of infusion therapy was required than in patients with normodynamic one.

Normodynamic type of blood circulation in the majority of patients of group STBI-BD transformed into hypodynamic type. Normodynamic type of blood circulation in 1 of the patients of group STBI transformed into hyperdynamic type on the following day. The rest of the patients of group STBI preserved the normodynamic type.

Hyperdynamic type of blood circulation was not observed in group STBI-BD patients (Figure 2) that apparently was connected with the hemodynamic monitoring carried out in the background of the ongoing vasopressor support. Nevertheless, one study [24] shows the hyperdynamic state in brain-dead patients.

To make a conclusion, normodynamic and hyperdynamic types of blood circulation are more favourable than hypodynamic type.

In 3 patients of 4 who were provided with ICP monitoring intracranial hypertension was characterized by the decrease of SVRI. The correction of doses of norepinephrine under SVRI monitoring was required to patients with a systemic vascular resistance deficit (15% patients) and with excess of systemic vascular resistance (31% patients) of group STBI.

All the patients of group STBI-BD were provided with vasopressor support to maintain the target parameters of MAP (70–90 mmHg). 12% of patients with a low systemic vascular resistance and 73% of patients with a high systemic vascular resistance required increase or decrease of norepinephrine under SVRI monitoring. Norepinephrine use in this category of patients was a reasonable choice. When combination of hypotension and bradycardia was observed, adrenaline was the choice. Apparently all patients of group STBI-BD had a combination of absolute and reliable hypovolemia that is why they needed vasoconstrictive drugs given in larger doses than to patients of group STBI. At the beginning period of brain death the increase of vasopressors doses leads to the sharp rise of SVRI. But at later periods of brain death SVRI does not respond so much to the increase of vasopressors doses (Variants STBI-BD-d, STBI-BD-e). These findings are consistent with other studies [25, 26] demonstrating that low systemic and pulmonary vascular resistances have been documented in the majority (75%) of brain dead subjects. In the late or end stage of brain death, hemodynamic deterioration and collapse led rapidly to arrest [24].

Our results demonstrated that hypovolemia is often detected in patients with isolated STBI in an acute period of traumatic disease and in brain dead donors. These findings are consistent with other studies [13, 27]. The hypovolemic state is difficult to assess without monitoring of central hemodynamic parameters.

One of the methods of preload determination which is commonly used nowadays is the measurement of CVP. During the research process normal values of central venous pressure (CVP, mmHg) were observed in all patients. Correlation analysis revealed no significant correlation between CVP and GEDI, a preload parameter. No significant correlation was revealed between CVP and ELWI either. These results are in agreement with other studies [28–31] and confirm the limited value of CVP both as an indicator of cardiac preload and as a predictor of fluid responsiveness. Therefore, monitoring of CVP cannot always determine adequate hemodynamic status of a patient (CVP can be within its normal values with normovolemia and hypovolemia). In the studies by Michard et al. [18, 32, 33], it was demonstrated that global end-diastolic volume (GEDV) but not CVP behaves as an indicator of cardiac preload.

It should be mentioned that not all cases with decreased GEDI SVV were increased. It may be related to the preserved patient initiation of the ventilator. Both GEDI and SVV may help in decision-making process concerning volume loading [28, 34, 35]. In cases of SVV limitation (arrhythmias, spontaneous breathing) GEDI as an indicator of cardiac preload can be applied [29, 30]. As it was shown in the studies of Michard at al., the lower is the preinfusion GEDI, the more marked are the hemodynamic effects of volume loading [18].

Positive response to volume loading which is characterized by the increase of SVI from its initial index by more than 15% was detected in 9 (69%) patients of 13 in group STBI and in 10 (66%) patients of 15 in group STBI-BD. SVI increased from its normal value by more than 10% in 11 (85%) patients of group STBI. So, in patients with detected hypovolemia and positive response to volume loading a pathogenetically based hemodynamic correction was carried out by the extension of infusion therapy.

Transpulmonary thermodilution enables the identification of patients with pulmonary edema (increased EVLW) as well as the quantification of pulmonary edema and its response to the ongoing treatment (e.g., fluid restriction/depletion) [21, 36, 37]. In addition, the assessment of pulmonary vascular permeability (PVPI) provides a better understanding of the pathophysiological mechanisms of hypoxemia.

Thus, the goal of management for hemodynamic status of the patients with STBI is to avoid hypovolemia by the means of careful fluid management, maintenance of blood pressure for reducing the risk of cerebral ischemia. The goals of management for the donor's hemodynamic status are to achieve normovolemia by volume expansion,

maintenance of blood pressure, and optimization of cardiac output so as to reach perfusion pressure and blood flow gradients that promote organ function with the least support of vasoactive drugs [26, 38]. Hemodynamic management requires continuous invasive monitoring to ensure that cardiac preload, afterload, and contractility are optimal [39]. Infusion therapy based on the estimation of routine hemodynamic parameters (blood pressure, heart rate, central venous pressure, daily fluid balance) could not prevent hypovolemia in the examinees and caused a high rate of sympathomimetic use in uncorrected volemic states [27]. Despite a limited scope of observations, our results confirmed the reasonability of hemodynamic monitoring which allows to determine the cause, carry out a timely correction of the observed disorders, and decrease the risk of complications associated with hypotension in patients with STBI and in patients with clinically established brain death. Further studies with more patients will help to reveal new features and regularities of central hemodynamic parameter changes in patients with STBI and to define the required measures for their correction.

5. Conclusion

In the present study, various types of hemodynamic reaction in patients with STBI were identified: normodynamic, hyperdynamic, and hypodynamic. Hyperdynamic type of blood circulation was not observed in patients with STBI and clinically established brain death. Monitoring of parameters of central hemodynamics (CI, SVI, SVRI, GEDI, SVV, GEF, CFI) allows carrying out pathogenetically based infusion, inotropic, vasopressor therapy in patients with STBI and in patients with clinically established brain death.

Acknowledgments

The authors are grateful to Dr. Nguyen Huu Tu, Associates Professor, Ph.D., Head of Department of Anaesthesiology and Critical Care, Hanoi Medical University and HMU Hospital, Dr. Nguyen Quoc Kinh, Associated Professor, Ph.D., Head of Department of Anaesthesiology and Critical Care, Viet-Duc Hospital, Vietnam, for encouragement of this study, and the staff of the ICU of Viet Duc Hospital, Vietnam, for assistance in carrying out the research.

References

[1] R. S. Cooke, B. P. McNicholl, and D. P. Byrnes, "Early management of severe head injury in Northern Ireland," *Injury*, vol. 26, no. 6, pp. 395–397, 1995.

[2] R. M. Chesnut, L. F. Marshall, M. R. Klauber et al., "The role of secondary brain injury in determining outcome from severe head injury," *Journal of Trauma*, vol. 34, no. 2, pp. 216–222, 1993.

[3] P. A. Jones, P. J. D. Andrews, S. Midgley et al., "Measuring the burden of secondary insults in head-injured patients during intensive care," *Journal of Neurosurgical Anesthesiology*, vol. 6, no. 1, pp. 4–14, 1994.

[4] D. A. Hill, K. J. Abraham, and R. H. West, "Factors affecting outcome in the resuscitation of severly injured patients," *Australian and New Zealand Journal of Surgery*, vol. 63, no. 8, pp. 604–609, 1993.

[5] G. Manley, M. M. Knudson, D. Morabito, S. Damron, V. Erickson, and L. Pitts, "Hypotension, hypoxia, and head injury: frequency, duration, and consequences," *Archives of Surgery*, vol. 136, no. 10, pp. 1118–1123, 2001.

[6] M. R. Fearnside, R. J. Cook, P. McDougall, and R. J. McNeil, "The Westmead Head Injury Project outcome in severe head injury. A comparative analysis of pre-hospital, clinical and CT variables," *British Journal of Neurosurgery*, vol. 7, no. 3, pp. 267–279, 1993.

[7] D. Deleu, M. A. Kettern, Y. Hanssens, S. Kumar, K. Salim, and F. Miyares, "Neurogenic stunned myocardium following hemorrhagic cerebral contusion," *Saudi Medical Journal*, vol. 28, no. 2, pp. 283–285, 2007.

[8] *Guidelines for the Management of Severe Traumatic Brain Injury*, Brain Trauma Foundation, 3rd edition, 2007.

[9] P. Curry, D. Viernes, and D. Sharma, "Perioperative management of traumatic brain injury," *International Journal of Critical Illness and Injury Science*, vol. 1, no. 1, pp. 27–35, 2011.

[10] H. S. Mangat, "Severe traumatic brain injury," *Continuum Lifelong Learning in Neurology*, vol. 18, no. 3, pp. 532–546, 2012.

[11] S. H. Haddad and Y. M. Arabi, "Critical care management of severe traumatic brain injury in adults," *Scandinavian Journal of Trauma, Resuscitation, and Emergency Medicine* vol. 20, article 12, 2012.

[12] A. I. Iaroshetskii, D. N. Protsenko, and B. R. Gel'fand, "Role of an anesthesiologist-resuscitation specialist in organ donation for transplantation," *Anesteziologiia i Reanimatologiia*, no. 3, pp. 4–8, 2010.

[13] R. Murugan, R. Venkataraman, A. S. Wahed et al., "Preload responsiveness is associated with increased interleukin-6 and lower organ yield from brain-dead donors," *Critical Care Medicine*, vol. 37, no. 8, pp. 2387–2393, 2009.

[14] R. Murugan, R. Venkataraman, A. S. Wahed et al., "Increased plasma interleukin-6 in donors is associated with lower recipient hospital-free survival after cadaveric organ transplantation," *Critical Care Medicine*, vol. 36, no. 6, pp. 1810–1816, 2008.

[15] G. Boulard, P. Guiot, T. Pottecher, and A. Tenailon, "Management of brain death cases from the perspective of organ donation," Proceedings of the Sfar/6STE/Agency of Biomedicine Conference Materials, Paris, France, 2005.

[16] G. Boulard, P. Guiot, T. Pottecher, and A. Tenailon, "Prise en charge des sujets en état de mort encéphalique dans l'optique d'un prélèvement d'organes," *Annales of French Anaesthesia and Resuscitation*, vol. 24, no. 7, pp. 836–843.

[17] O. Gödje, K. Höke, A. E. Goetz et al., "Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability," *Critical Care Medicine*, vol. 30, no. 1, pp. 52–58, 2002.

[18] F. Michard, S. Alaya, V. Zarka, M. Bahloul, C. Richard, and J. L. Teboul, "Global end-diastolic volume as an indicator of cardiac preload in patients with septic shock," *Chest*, vol. 124, no. 5, pp. 1900–1908, 2003.

[19] G. D. Rocca, M. G. Costa, and P. Pietropaoli, "How to measure and interpret volumetric measures of preload," *Current Opinion in Critical Care*, vol. 13, no. 3, pp. 297–302, 2007.

[20] S. G. Sakka, C. C. Rühl, U. J. Pfeiffer et al., "Assessment of cardiac preload and extravascular lung water by single

transpulmonary thermodilution," *Intensive Care Medicine*, vol. 26, no. 2, pp. 180–187, 2000.

[21] S. G. Sakka, M. Klein, K. Reinhart, and A. Meier-Hellmann, "Prognostic value of extravascular lung water in critically III patients," *Chest*, vol. 122, no. 6, pp. 2080–2086, 2002.

[22] H. Belzberg, C. C. J. Wo, D. Demetriades, and W. C. Shoemaker, "Effects of age and obesity on hemodynamics, tissue oxygenation, and outcome after trauma," *Journal of Trauma*, vol. 62, no. 5, pp. 1192–1200, 2007.

[23] T. P. Nicholls, W. C. Shoemaker, C. C. J. Wo, J. P. Gruen, A. Amar, and A. B. C. Dang, "Survival, hemodynamics, and tissue oxygenation after head trauma," *Journal of the American College of Surgeons*, vol. 202, no. 1, pp. 120–130, 2006.

[24] H. Belzberg, W. C. Shoemaker, C. C. J. Wo et al., "Hemodynamic and oxygen transport patterns after head trauma and brain death: implications for management of the organ donor," *Journal of Trauma*, vol. 63, no. 5, pp. 1032–1042, 2007.

[25] V. Gravame, M. Cardillo, G. Paganoni et al., "Systemic and pulmonary vascular resistance in brain death," *Minerva Anestesiologica*, vol. 66, no. 4, pp. 217–223, 2000.

[26] L. Mascia, I. Mastromauro, S. Viberti, M. Vincenzi, and M. Zanello, "Management to optimize organ procurement in brain dead donors," *Minerva Anestesiologica*, vol. 75, no. 3, pp. 125–133, 2009.

[27] I. V. Titova, S. S. Petrikov, A. A. Solodov, and V. V. Krylov, "Systemic hemodynamic disorders in critically ill patients with intracranial hemorrhages," *Anesteziologiia i Reanimatologiia*, no. 4, pp. 24–28, 2010.

[28] T. Mutoh, K. Kazumata, T. Ishikawa, and S. Terasaka, "Performance of bedside transpulmonary thermodilution monitoring for goal-directed hemodynamic management after subarachnoid hemorrhage," *Stroke*, vol. 40, no. 7, pp. 2368–2374, 2009.

[29] C. Reuse, J. L. Vincent, and M. R. Pinsky, "Measurements of right ventricular volumes during fluid challenge," *Chest*, vol. 98, no. 6, pp. 1450–1454, 1990.

[30] L. N. Diebel, R. F. Wilson, M. G. Tagett, and R. A. Kline, "End-diastolic volume: a better indicator of preload in the critically ill," *Archives of Surgery*, vol. 127, no. 7, pp. 817–822, 1992.

[31] M. Lichtwarck-Aschoff, R. Beale, and U. J. Pfeiffer, "Central venous pressure, pulmonary artery occlusion pressure, intrathoracic blood volume, and right ventricular end-diastolic volume as indicators of cardiac preload," *Journal of Critical Care*, vol. 11, no. 4, pp. 180–188, 1996.

[32] F. Michard and J. L. Teboul, "Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence," *Chest*, vol. 121, no. 6, pp. 2000–2008, 2002.

[33] F. Michard and A. Perel, "Management of circulatory and respiratory failure using less invasive hemodynamic monitoring," in *Yearbook of Intensive Care and Emergency Medicine*, J. L. Vincent, Ed., pp. 508–520, Springer, Berlin, Germany, 2003.

[34] G. Marx, T. Cope, L. McCrossan et al., "Assessing fluid responsiveness by stroke volume variation in mechanically ventilated patients with severe sepsis," *European Journal of Anaesthesiology*, vol. 21, no. 2, pp. 132–138, 2004.

[35] H. Berkenstadt, N. Margalit, M. Hadani et al., "Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery," *Anesthesia and Analgesia*, vol. 92, no. 4, pp. 984–989, 2001.

[36] F. Michard, A. Schachtrupp, and C. Toens, "Factors influencing the estimation of extravascular lung water by transpulmonary thermodilution in critically ill patients," *Critical Care Medicine*, vol. 33, no. 6, pp. 1243–1247, 2005.

[37] M. Y. Kirov, V. V. Kuzkov, and L. J. Bjertnaes, "Extravascular lung water in sepsis," in *Yearbook of Intensive Care and Emergency Medicine*, J. L. Vincent, Ed., pp. 449–461, Springer, Berlin, Germany, 2005.

[38] D. W. McKeown, R. S. Bonser, and J. A. Kellum, "Management of the heartbeating brain-dead organ donor," *British Journal of Anaesthesia*, vol. 108, supplement 1, pp. i96–i107, 2012.

[39] D. J. Powner, "Treatment goals during care of adult donors that can influence outcomes of heart transplantation," *Progress in Transplantation*, vol. 15, no. 3, pp. 226–232, 2005.

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 597932, 9 pages
doi:10.1155/2012/597932

Review Article

Goal-Directed Mechanical Ventilation: Are We Aiming at the Right Goals? A Proposal for an Alternative Approach Aiming at Optimal Lung Compliance, Guided by Esophageal Pressure in Acute Respiratory Failure

Arie Soroksky[1,2] and Antonio Esquinas[3]

[1] *Intensive Care Unit, E. Wolfson Medical Center, Halohamim st 62, 58100 Holon, Israel*
[2] *Sackler Faculty of Medicine, University of Tel Aviv, 69978 Tel Aviv, Israel*
[3] *Intensive Care Unit, Hospital Morales Meseguer, Avenida Marqués de Los Velez s/n, 30500 Murcia, Spain*

Correspondence should be addressed to Arie Soroksky, soroksky@gmail.com

Received 30 June 2012; Revised 12 August 2012; Accepted 13 August 2012

Academic Editor: Mikhail Y. Kirov

Patients with acute respiratory failure and decreased respiratory system compliance due to ARDS frequently present a formidable challenge. These patients are often subjected to high inspiratory pressure, and in severe cases in order to improve oxygenation and preserve life, we may need to resort to unconventional measures. The currently accepted ARDSNet guidelines are characterized by a generalized approach in which an algorithm for PEEP application and limited plateau pressure are applied to all mechanically ventilated patients. These guidelines do not make any distinction between patients, who may have different chest wall mechanics with diverse pathologies and different mechanical properties of their respiratory system. The ability of assessing pleural pressure by measuring esophageal pressure allows us to partition the respiratory system into its main components of lungs and chest wall. Thus, identifying the dominant factor affecting respiratory system may better direct and optimize mechanical ventilation. Instead of limiting inspiratory pressure by plateau pressure, PEEP and inspiratory pressure adjustment would be individualized specifically for each patient's lung compliance as indicated by transpulmonary pressure. The main goal of this approach is to specifically target transpulmonary pressure instead of plateau pressure, and therefore achieve the best lung compliance with the least transpulmonary pressure possible.

1. Introduction

Patients with severe respiratory failure exhibiting decreased respiratory system compliance with hypoxemia or carbon dioxide retention are often difficult to ventilate and or oxygenate with current guidelines that limit applied plateau pressure. Furthermore, applying mechanical ventilation while limiting plateau pressure without assessment of respiratory system mechanics may result in application of inappropriate positive end expiratory pressure (PEEP) and inspiratory pressures.

Thus, while these guidelines recommend a certain limit of plateau pressure, they do not take into consideration chest wall mechanics, which can only be assessed by partitioning respiratory system into its components by esophageal balloon and assessment of pleural pressure.

Without partitioning of the respiratory system into its components, one cannot ascertain and identify the factors contributing to low respiratory system compliance.

Identifying the dominant factor affecting respiratory system compliance by measuring transpulmonary pressure may better direct and optimize mechanical ventilation. Thus, instead of limiting mechanical ventilation by plateau pressure, PEEP and Inspiratory pressure adjustment would be individualized specifically for each patient's lung compliance as indicated by transpulmonary pressure.

The main goal of this approach is to specifically target and achieve best possible lung compliance by assessment

of transpulmonary pressure instead of plateau pressure and adjust PEEP according to chest wall and lung compliance instead of total respiratory system compliance.

2. The Validity of Esophageal Balloon as a Surrogate of Pleural Pressure

Historically, esophageal balloon has been used for several decades to estimate pleural pressure. The assumption that esophageal pressure reflects pleural pressure is based on the notion that pressure in the adjacent pleura is transmitted to the esophagus [1]. This is supported by several historical studies demonstrating reasonable correlation between pleural and esophageal pressures [2–4]. However, pressure within the pleural space is not uniform. The pressure in the dependent and basal regions close to the diaphragm is greater than in the upper regions of the thoracic cage. This nonuniform pleural pressure in the upright patient exerts nonuniform pressure on the esophagus as well. Thus, in the upright position pressure measured within the esophagus varies according to the level or position of the catheter within the esophagus [5]. However, in the supine critically ill and mechanically ventilated patient pressure in the pleural space distributes differently than in the upright position. It is thought that in the supine position esophageal pressure is higher than in the upright position with resulting decreased lung compliance [5, 6]. The increase in pleural pressure in supine position is mainly caused by mediastinal structure weight that distributes differently than in the prone position. The mid third of the esophagus is thought to be the most representative and reflect most closely the effective pleural pressure [7].

Effective pleural pressure is the pressure that results from actual flow and pressure applied to the respiratory system, and thought to represent the combined effects of the different pressures found in different regions of the pleural space. Thus, although effective pleural pressure is not as accurate as pressure measurement of a specific region within the pleural space, in the clinical scenario, it does give us a reasonable clinical approximation of the average pleural pressure.

Consequently, measurement of esophageal pressure may be used as a rough estimate of pleural pressure. However, such an inference bears with its limitations, which have to be taken into account when interpreting measurements of esophageal pressure. These include the fact that in the clinical setup of critically ill patient who is mechanically ventilated and therefore in the supine or semirecumbent position, the weight of mediastinal structures such as the heart has to be accounted for. In a report by Washko et al. [5], postural changes on esophageal pressure measurements were studied on 10 healthy subjects. They showed that mediastinal structures added 3 ± 2 cm H_2O to the measured esophageal pressure. However, it should be noted that with increasing airway pressure, there is a possibility for a concomitant decrease of superimposed pressure [8]. This could partly be explained by a possible shift of blood out of the thorax with increasing airway and pleural pressure.

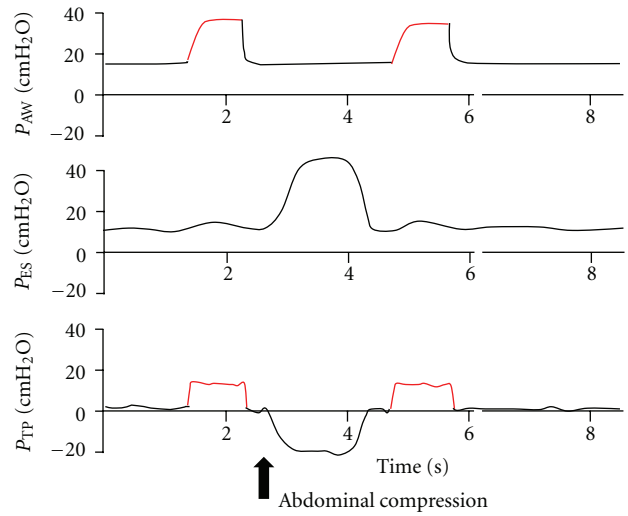


Figure 1: Pressure tracing of esophageal balloon with its tip in the stomach (60 to 70 cm below the incisors). Black arrow indicates gentle compression of the abdomen by the examiner. Catheter position in the stomach is also indicated by the smooth nature of the pressure tracing of the esophageal balloon and the lack of the effect of heart beat on the pressure tracing. P_{Aw} = airway opening pressure, P_{ES} = esophageal pressure, P_{TP} = transpulmonary pressure.

Thus, the appropriate correction factor that should be applied when we interpret esophageal pressure measurements is still controversial. Nevertheless, Talmor et al. used a similar correction in two recent reports [9, 10]. They subtracted 3 cm H_2O for the possible weight of the heart, and another 2 cm H_2O to correct for the effects of air volume within the esophageal balloon catheter. Thus, in their studies, in order to better approximate pleural pressure, 5 cm H_2O was subtracted from the measured esophageal pressure.

Weight from mediastinal structures is not the only factor that may influence accurate estimation of pleural pressure. Other factors may affect esophageal pressure measurements. These include muscle contraction that can affect intrathoracic pressures in a regional way depending on the groups of muscles that are active [11], catheter position within the esophagus [2], active tension in the walls of the esophagus [12], uneven distribution of pleural surface pressure, and esophageal spasm or contraction.

3. Clinical Interpretation of Esophageal Balloon Measurements

The proper interpretation of esophageal balloon measurements begins with correct esophageal catheter insertion. We usually insert the catheter well beyond 40 to 50 cm below the incisors. The purpose of advancing the catheter beyond 50 cm below the incisors is to assure that catheter tip is well within the stomach. This can be ascertained by gentle compression of the abdomen and inspection of esophageal pressure waveform (Figure 1).

Once a positive inflection of esophageal pressure waveform is noticed with abdominal compression, the catheter

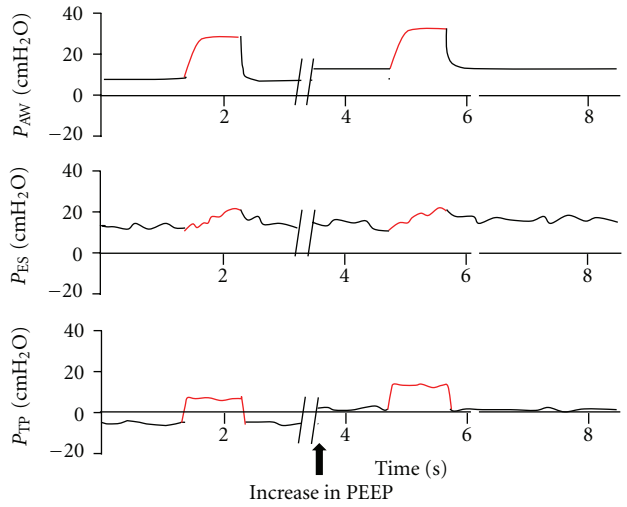


FIGURE 2: Negative transpulmonary pressure at end-expiration may subject the lungs to cyclic collapse. Black arrow indicates the point where PEEP was raised to a level that would ensure a slightly positive end-expiratory transpulmonary pressure. P_{Aw} = airway opening pressure, P_{ES} = esophageal pressure, P_{TP} = transpulmonary pressure.

is then gently withdrawn cephalad until cardiac pulsations, sometimes "saw tooth" like in appearance, simultaneous with heart beat can be noticed on the pressure tracing. This usually happens when the catheter is right adjacent to the heart, and its tip is about 40 cm from the incisors. At this level, the esophageal balloon is usually located at mid to lower third of the esophagus. Further confirmation of proper positioning of esophageal balloon can be obtained by performing the occlusion test [7, 13], in which the patient makes inspiratory or expiratory effort during airway occlusion and observing similar changes in esophageal and airway pressures.

However, occlusion test cannot be performed on paralyzed patients, in such cases for verification of correct catheter position, we may need to relay only on waveform pressure tracing interpretation.

After verifying a correct esophageal balloon placement, measuring esophageal pressure at end expiration and end inspiration is most informative and allows us to partition respiratory system into its components.

The value measured at end expiration is calculated by subtracting end-expiratory esophageal pressure (EEPes) from airway pressure (Pao). It is mostly influenced by the applied external PEEP and by the chest wall effect. Ideally, this value should be slightly positive. A negative value indicates that the applied PEEP is actually lower than pleural pressure. This may be associated with cyclic alveolar lung units that collapse at end expiration. Thus, adjustment of PEEP to ensure positive end expiratory pressure may prevent the damage associated with the shearing forces of cyclic inflation and deflation (Figure 2).

Furthermore, PEEP adjustment guided by esophageal pressure measurements allows us to fine-tune it to ensure that the applied PEEP be at least in the magnitude of the estimated pleural pressure, while at the same time avoiding a too high value that could cause over stretching.

Similarly, transpulmonary pressure (PL) measured at end inflation reflects the actual distending pressure acting on the lungs. Normally, it should not exceed 20 to 25 cm H_2O.

In patients with high pleural pressure a low PL can usually be found. This can easily be appreciated by the following equation.

$$P_{PL} = P_{AW} - \frac{E_{CW}}{E_{TOT}}, \quad (1)$$

where as P_{PL} is Pleural pressure, P_{AW} is the airway opening pressure, and E_{CW} and E_{TOT} are chest wall elastance and total elastance, respectively. As an example, in a patient with high PIP of 30 cm H_2O, without measuring pleural pressure, one may assume that the lungs are subjected to over distension [14, 15]. However, suppose that upon measurement of esophageal pressure, a pleural pressure of 20 cm H_2O is found, in such a case there would be a low transpulmonary pressure of 10 cm H_2O. Theoretically, in such a patient, identifying a high pleural pressure as the cause of the high PIP gives us the option to increase the limit of PIP beyond the traditional plateau pressure of 30 cm H_2O. By doing so, even though the traditional PIP upper limit of 30 cm H_2O is exceeded, the lungs are still subjected to a distending pressure that is well within the safe and accepted limits of the recommended transpulmonary pressure. This practice however should be exercised with caution, and the recommended 6 ml/kg of tidal volume should not be exceeded.

Analyzing the shape of the esophageal pressure tracing may provide additional information. In a patient with "stiff lung" airway pressure is only partially transmitted to the pleura, and in severe cases may not be transmitted at all (Figure 3). This is in opposite of very compliant lungs where a clear difference between end-expiratory and end-inspiratory pressure can be observed. This pressure difference is the actual pressure that is transmitted to the pleura (Figure 3).

An interesting phenomenon that we have observed during the routine use of esophageal catheters is high transpulmonary pressures during patient-initiated spontaneous breath (Figure 4). A large inspiratory effort that initiates assisted pressure support delivery may result in large transpulmonary pressure. As there is no, or only limited patient effort during mandatory breath, this phenomenon is not observed during ventilator-initiated mandatory breath. The same phenomenon was recently described by Yoshida et al. [16], in an experimental model of acute lung injury in rabbits. Similarly to our observation, Yoshida and his colleagues point to a combination of mandatory breath superimposed on a strong spontaneous breathing effort which in spite delivery of tidal volume results in high transpulmonary pressure, which may promote lung damage.

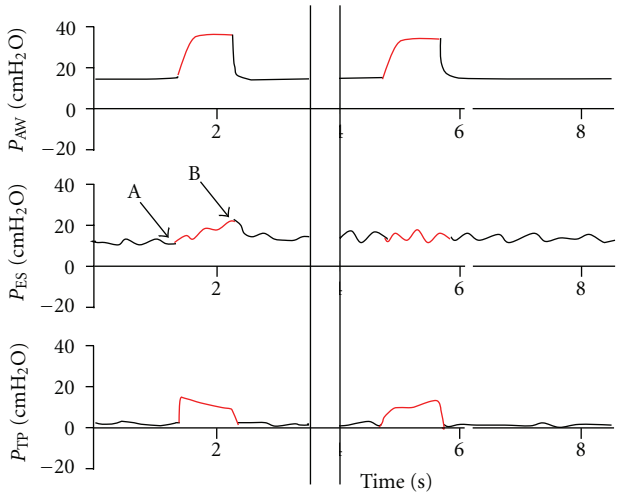


Figure 3: The left part of the pressure tracing shows a compliant lung that transmits part of the applied airway pressure to the pleura. The difference in pressure between points A and B represents the actual pressure transmitted to the pleura. The right part of the pressure tracing demonstrates a noncompliant lung that transmits little or no pressure to the pleura. P_{Aw} = airway opening pressure, P_{ES} = esophageal pressure, P_{TP} = transpulmonary pressure.

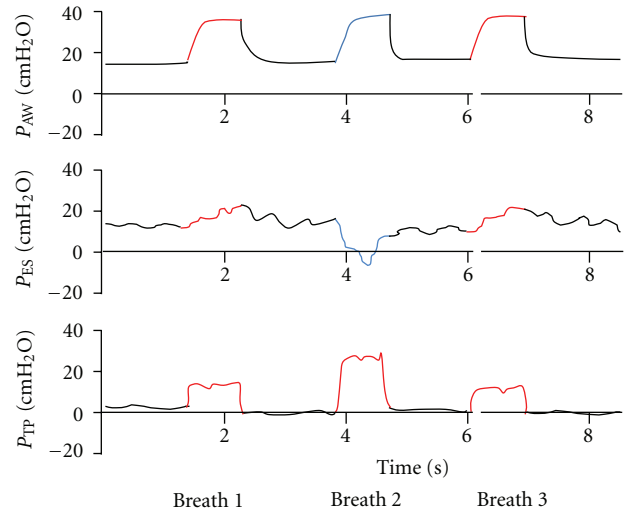


Figure 4: Pressure tracing demonstrating mandatory breaths delivered with inspiratory pressure of 20 cm H_2O (breaths number 1 and 3). The second breath is initiated by the patient and is assisted with pressure support of 20 cm H_2O by the ventilator. The large inspiratory effort by the patient (breath 2) results in a negative deflection on the esophageal pressure tracing. This negative deflection generates high transpulmonary pressure, in this example close to 30 cm H_2O. P_{Aw} = airway opening pressure, P_{ES} = esophageal pressure, P_{TP} = transpulmonary pressure.

4. Clinical Evidence for the Use of Esophageal Balloon in Mechanically Ventilated Patients

The use of esophageal balloon in the clinical setup has not been described extensively in mechanically ventilated patients. Historically, its use has been cumbersome, not always reproducible, not widely available, and therefore, it was mainly used for research purposes.

Thus, it is only in the last six years that studies were published reporting mainly case series of patients whose mechanical ventilation was guided by esophageal balloon pressure measurements with assessment of pleural pressure. In the first large series, Talmor and his colleagues [10] described the feasibility of esophageal balloon catheter use in seventy patients with acute respiratory failure of all causes.

The decision to insert esophageal balloon was based on clinical grounds, and there were no systematic selection criteria. In this case series, Pes at end-expiration averaged 17.5 ± 5.7 cm H_2O and 21.2 ± 7.7 cm H_2O at end-inflation. Interestingly, there was no clear association between these measured esophageal pressures and body mass index or chest wall elastance. Estimated transpulmonary pressure (PL) was positive in most patients and was 1.5 ± 6.3 cm H_2O at end-expiration, and 21.4 ± 9.3 cm H_2O at end-inflation. Interestingly, PL at end-expiration was significantly correlated with PEEP. However, only 24% of the variance in PL was explained by airway opening pressure (P_{ao}), and 52% was due to variation in P_{es}. These findings demonstrated the significance of chest wall as a major factor contributing to low respiratory system compliance. Two years later, Talmor et al. reported on another trial [9]. In this study, patients with ARDS were randomly assigned to be mechanically ventilated with PEEP adjustments guided by esophageal pressure, or according to ARDS Net recommendations (control group). The primary endpoint was improvement in oxygenation. The secondary endpoints were respiratory system compliance and patient outcomes. The study was stopped prematurely by the safety committee due to significantly large differences in oxygenation between the two groups, after recruiting only 61 patients. The $PaO_2 : FiO_2$ at 72 hours was 88 mm Hg higher in patients treated with mechanical ventilation with esophageal balloons than in control patients (95% confidence interval, 78.1 to 98.3; $P = 0.002$). Similarly, respiratory system compliance was improved and was significantly better in the esophageal pressure-guided group at 24, 48, and 72 hours. This improvement can largely be attributed to the generally higher values of PEEP applied in the esophageal pressure-guided group (17 ± 6 versus 10 ± 4, $P < 0.001$).

Furthermore, It should be noted that by 72 hours, transpulmonary end expiratory pressure was negative in the control group (0.1 ± 2.6 versus −2.0 ± 4.7, $P < 0.06$), whereas in the esophageal pressure guided group, this value was positive, this was achieved by significant increase in PEEP. Mortality, a secondary outcome measure, had a trend toward a better outcome in the esophageal pressure guided group, but it did not reach statistical significance.

Recently Grasso et al. [17] described 14 patients with severe ARDS due to influenza who were referred to their center for possible treatment with ECMO. Upon measurements of esophageal pressure, half of the patients were found to have high transpulmonary pressure (27.2 ± 1.2 cm H_2O), and they were all treated with ECMO.

However, the other half of the patients were found to have a low end-inspiratory transpulmonary pressure (16.6 ± 2.9 cm H_2O), thus allowing the increase of PEEP with improvement in respiratory parameters (improved oxygenation index from 37.4 ± 3.7 to 16.5 ± 1.4, $P = 0.0001$) and eventually the successful management of these patients conservatively without ECMO. This example only demonstrates how knowledge of pleural pressure may actually change patient treatment.

The main limitation of all these reports is the primary outcome, which is mostly the rate of improvement in oxygenation and lung compliance. By now, we already know that improvement in oxygenation, a main outcome measure in these studies, is not necessarily associated with improved patient survival. Although in the study of Talmor et al. [9], there was a trend towards improved survival in the esophageal pressure guided group, probably due to small sample size, it did not reach statistical significance. Thus, for a study to achieve a statistical significance for a major outcome such as improved survival, at least a few hundred patients, all monitored with esophageal balloon, have to be recruited. Such an immense effort can only be achieved with an international multiple center study. However, since the use of esophageal balloon is still not a common practice in many ICUs, there is no forecast for such an effort in the near future.

5. Are We Aiming at the Right Goals? Should We Change Our Practice?

In the last two decades, significant progress has been made in our understanding of the implications of inappropriate mechanical ventilation. Patient exposure to high inspiratory pressures and high tidal volumes is now recognized as major risk factors for lung damage. In addition, application of inappropriately low or high PEEP values may also contribute to inappropriate ventilation with worsening hypoxemia and increase in shunt fraction.

The recognition that limiting inspiratory pressure may decrease mortality has led to the development of lung protective ventilation. Although this approach may offer a mortality benefit in the general population of mechanically ventilated patients, it does not address individual patients lung and chest wall mechanics. Therefore, treating individual patients with a generalized approach ignores variations between patients and does not take into account different patient lung and chest wall mechanics.

Based on the few reports published in the last few years [9, 10, 17], we have adopted an alternative approach, whereby in our ICU, an esophageal balloon is routinely being used in patients with severe respiratory failure for assessment of pleural pressure. The use of esophageal balloon has been further promoted by the recent availability of commercially available esophageal nasogastric catheters, some of which are even equipped with an internal lumen that allows simultaneous nasogastric feeding.

In their study, Talmor et al. [9] reported that in approximately one-third of the patients, the balloon could not be passed into the stomach, and esophageal placement was confirmed only by the presence of a cardiac artifact on the pressure tracing. However, with the use of recently commercially available nasogastric esophageal balloon catheters which are thicker, less pliable, and with internal lumen for nasogastric feeding, we are now able to use esophageal pressure monitoring for prolonged periods while at the same time continue feeding these patients.

There is a paucity of information on when to use esophageal balloon and on what patients. The existing reports did not use clear inclusion criteria. Therefore, there are no clear definitions or recommendations. However, our group has developed systematic clinical criteria that could guide patient selection for esophageal balloon insertion. We do not use esophageal balloon in every patient who is mechanically ventilated. Instead, we use esophageal balloon only in the most severe cases of respiratory failure.

To be eligible for esophageal balloon insertion, a prerequisite of high-peak inspiratory pressure (plateau pressure of 25 to 30 cm H_2O) has to be present, and at least one of the following four severity criteria has to be met.

(1) Low total respiratory system compliance (C_T), defined as less than 40 ml/cm H_2O.

(2) P/F ratio of less than 300.

(3) Need for a PEEP greater than 10 cm H_2O to maintain SaO_2 of >90%.

(4) PCO_2 over 60 mm Hg, or PH less than 7.2 that is attributed to respiratory acidosis.

With the selection of appropriate patients, we may see a continued spread and increased use of esophageal balloon in the near future. Together with the already available published evidence indicating a beneficial effect of esophageal balloon pressure measurements on oxygenation and lung compliance raise important questions.

(i) Are the Acute Respiratory Distress Syndrome Network (ARDSNet) recommendations [30] appropriate for all patients?

(ii) Should we continue and ignore large variations in lung and chest wall mechanics in individual patient?

(iii) Furthermore, while we mechanically ventilate patients with severe respiratory failure, are we aiming at the right goals? In other words, is limiting plateau pressure to 30 cm H_2O without taking into account lung and chest wall mechanics is a good and sound physiological practice?

The answer to all these questions is probably no.

With regard to ARDSNet recommendations, many feel that they are reasonable recommendations for a general population of mechanically ventilated patients who are not the most severe ones. Table 1 summarizes the studies on mechanical ventilation strategies in ARDS patients in the last decade.

Table 2 summarizes the few meta-analysis examining ventilation strategies in ARDS. Among the many studies examining the most appropriate PEEP in ARDS patients several stand out in terms of sample size and quality. For

Table 1: Randomized controlled trials of ARDS ventilation strategies. (last 10 year-humans) years 2000–2012.

Author/year/ref	Mechanical ventilation strategy	Study aims	Major observations
Hodgson et al., 2011, [18]	Recruitment PEEP and PMV	Open-lung strategy titrated PEEP and targeted and low airway pressures	Open-lung strategy was associated with greater amelioration in some systemic cytokines, improved oxygenation, and lung compliance over seven days.
Chung et al., 2010, [19]	HFPV	HFPV and low tidal volume ventilation	Acidosis and hypercapnia induced by VT reduction and increase in PEEP at constant *P* (plat) were associated with impaired right ventricular function and hemodynamics despite positive effects on oxygenation and alveolar recruitment.
Mekontso Dessap et al., 2009, [20]	Sighs superimposed on lung PMV	Impact of acute hypercapnia and augmented positive	Sighs superimposed on lung-protective mechanical ventilation with optimal PEEP improved oxygenation and static compliance in patients with early ALI/ARDS.
Badet et al., 2009, [21]	Recruitment maneuvers on lung PMV	Comparison of optimal PEEP and recruitment maneuvers, lung-protective mechanical ventilation	Sighs superimposed on lung-protective mechanical ventilation with optimal PEEP improved oxygenation and static compliance.
Mercat et al., 2008, [22]	Recruitment maneuvers	PEEP strategy for setting PEEP	Increasing alveolar recruitment while limiting hyperinflation did not significantly reduce mortality. However, it did improve lung function and reduced the duration of mechanical ventilation and duration of organ failure.
Meade et al., 2008, [23]	PMV with low VT	Strategy using low tidal volumes, recruitment maneuvers	Open lung resulted in no significant difference in all-cause hospital mortality and high PEEP or barotrauma compared with an established low-tidal-volume protocoled ventilation strategy.
Wolthuis et al., 2008, [24]	Low VT and PMV	Lower Tv and PEEP prevent pulmonary inflammation in patients without preexisting ALI	Lower VT and PEEP may limit pulmonary inflammation.
Pachl et al., 2006, [25]	HFOV	Normocapneic HFOV affects differently extra pulmonary and pulmonary forms of ARDS	HFOV recruits and thus it is more effective in ARDS.

ALI: acute lung injury, ARDS: acute respiratory distress syndrome, HFOV: High-frequency oscillatory ventilation, HFPV: high-frequency pulmonary ventilation, *P* (plat): Plateau pressure, PEEP: positive end expiratory pressure, PMV: protective mechanical ventilation, and VT: tidal volume.

example, these studies [31–33] investigated the effects of higher PEEP values in ARDS patients and failed to show improved survival. A common finding to these studies is the improvement in outcome measures such as oxygenation, hospital stay, and perhaps length of mechanical ventilation. However, survival, a major outcome in these studies, was not affected by higher PEEP values.

Conversely, in patients with severe ARDS, the recommendations of ARDSNet may result in under treatment in terms of applied PEEP which according to the ARDSNet algorithm in these patients may be too low. This was shown in a meta-analysis of three randomized studies [34]. Treatment with higher versus lower levels of PEEP was not associated with improved hospital survival. However, a subgroup analysis on patients with severe ARDS defined by P/F ratio <200 did show improved survival in patients treated with higher PEEP values, with mortality of 34.1% versus 39.1% (adjusted RR, 0.90; 95% CI, 0.81–1.00; $P = .049$).

Table 2: Meta-analysis studies of ARDS ventilation and strategies (last year 10 year-humans) years 2000–2012.

Author/year/ref	ARDS-Mechanical ventilation strategies	Major results	Study limitations	Recommendations
Burns et al., 2011 [26] Petrucci and Iacovelli, 2007 [27]	Pressure and volume limited ventilation	PVL strategies reduce mortality. Mortality is significantly reduced at day 28 and at the end of hospital stay. Increment of paralytic agents.	Clinical heterogeneity, such as different lengths of follow-up and higher plateau pressure in control arms in two trials, make the interpretation of the combined results difficult.	There was insufficient evidence concerning morbidity and long term outcomes.
Putensen et al., 2009 [28]	Low VT strategy and outcomes	Available evidence from a limited number of RCTs shows better outcomes with routine use of low VT but not high PEEP ventilation in unselected patients with ARDS or acute lung injury.	limited number of RCTs	Best outcomes with routine use of low VT but not with high PEEP.
Hodgson et al., 2009 [29].	Recruitment maneuvers	Recruitment maneuvers significantly increased oxygenation above baseline levels for a short period of time in four of the five studies that measured oxygenation.	There were insufficient data on length of ventilation or hospital stay to pool results.	There is no evidence to make conclusions on whether recruitment maneuvers reduce mortality or length of ventilation in patients with ALI or ARDS.

ARDS: adult respiratory distress syndrome, PVL: pressure volume limited. VT: tidal volume.

Thus, patients with milder acute lung injury (paO_2/FiO_2 ratio > 200) treated with higher PEEP had a trend toward harm.

This suggests that patients with low or normal pleural pressure who are exposed to higher PEEP values, as a result, may be subjected to higher transpulmonary pressures with possible lung over inflation, that may promote ventilator-induced lung injury, barotraumas, or decreased cardiac output.

Since pleural pressure was not assessed in these studies, there is a possibility that part of the beneficial effect of raising PEEP was due to offsetting a negative transpulmonary pressure at end expiration (EXPtp). This possibility is supported by previous reports [9, 10] demonstrating improved oxygenation and lung compliance when end-expiratory transpulmonary pressure was kept positive. The common belief is that by keeping EXPtp positive, we may prevent cycling collapse with deflations at end expiration, and thus derecruitment of alveolar lung units at end expiration.

Therefore, a recommendation suggesting a common PEEP value to all patients may result in over inflation in patients with low pleural pressure, and at the other end of the spectrum may ignore and miss those patients with high pleural pressure due to chest wall effect. These may be the patients with abdominal surgery, obese patients, and patients with severe chest wall edema. Common to all these patients is a phenomena where abdominal content pushes the diaphragm cephalad while encroaching upon the lungs. This results in increased pleural pressure due to chest wall effect and is usually associated with low transpulmonary pressure.

Thus, while these patients demonstrate high-peak Inspiratory pressures (PIPs) with decreased total respiratory system compliance. The actual transpulmonary pressure is low, and usually well below the upper limit of 25 cm H_2O.

In fact, in the study of Talmor et al. [9], the average end inspiratory transpulmonary pressure (EIPtp) was 8.6 ± 5.4 in the conventional treatment group, and 7.9 ± 6.0 in the esophageal pressure guided group. These relatively low EIPtp values suggest that in at least some patients with high PIP, the dominant component responsible for the high PIP is the high pleural pressure. Thus, knowledge of lung mechanics allows us to raise PEEP and inspiratory pressure. Therefore, instead of aiming at a plateau pressure of 30 cmH_2O, we are now able to target specifically lung compliance. By adopting this approach, Talmor et al. [9] raised PEEP without necessarily increasing significantly PIP. In their study, the average plateau pressure in the esophageal-guided group was not significantly greater than in the conventional group. This effect was probably achieved by increasing PEEP which resulted in improved lung compliance.

Lastly, are we aiming at the right goals? Should a plateau pressure of 30 cm H_2O be our limit? Based on the few reports available, the answer is probably no, or at least not for everybody.

Based on these reports and on our experience, we believe that many mechanically ventilated patients will be able to be managed by the standard ARDSNet approach. These

patients usually exhibit acceptable total respiratory system compliance and reasonable oxygenation, thus negating the need for high PEEP which in this group of patients is not beneficial [34]. However, a significant proportion of patients may present with severe ARDS characterized by low total respiratory system compliance and with high PIPs. These patients should be suspected to have a chest wall effect.

However, without partitioning of the respiratory system into its components by measuring esophageal pressure with assessment of pleural pressure we may not appreciate the true contribution of chest wall on lung mechanics. In such patients, without identifying the factors contributing to low respiratory system compliance, we may apply inappropriately low levels of PEEP.

While considering the approach of esophageal pressure monitoring for guiding mechanical ventilation, some limitations of this approach should be familiar and acknowledged. Firstly, it should be noted that the few available reports that evaluated PEEP adjustments based on esophageal pressure were performed mostly on patient with lung lesions that are more diffuse in their nature, such as ARDS or bilateral pneumonia. Therefore, in patients with pulmonary lesions involving one lung, such as one-sided pneumonia, the effects of adjustment of PEEP based on esophageal pressure in these patients are still unknown. Secondly, as with any other instance when high PEEP values are applied, the hemodynamic side effect of exposing patients to high positive pressure should be kept in mind and hemodynamic compromise should be identified promptly, especially in hypovolemic patient.

In conclusion, we believe that the standard ARDSNet approach will suffice for most of the mildly ventilated patient. In these patients, a plateau pressure limit of 30 cm H_2O is an acceptable limit. However, in patients with severe ARDS and low compliance, esophageal balloon and bedside assessment of pleural pressure should be routinely used when available. This approach allows us to partition the respiratory system into its components allowing us to apply the most appropriate PEEP and inspiratory pressure for each individual patient. Thus, with this individual patient approach, we are aiming at a target that results in best lung compliance. And instead a plateau pressure, our limits should be end inspiratory transpulmonary pressure that is lower than 25 cm H_2O, while at the same time keeping a slightly positive end expiratory transpulmonary pressure.

Finally, the last major advancement in the field of mechanical ventilation was based on physiologic research performed from many committed investigators who provided the pathophysiologic knowledge of ventilator-induced lung injury. The interpretation of these studies has led trials such as the ARDSNet published in 2000, and eventually to the development of lung protective ventilation approach.

We hope that the next major leap in mechanical ventilation will be an international effort similar in size to the ARDSNet that would compare in patients with severe ARDS, the general approach of ARDSNet with an approach that adjusts mechanical ventilation individually, tailored to each patient as guided by esophageal balloon measurements.

References

[1] J. Milic-Emili, J. Mead, J. M. Turner, and E. M. Glauser, "Improved technique for estimating pleural pressure from esophageal balloons," *Journal of Applied Physiology*, vol. 19, pp. 207–211, 1964.

[2] B. D. Higgs, P. K. Behrakis, D. R. Bevan, and J. Milic Emili, "Measurement of pleural pressure with esophageal balloon in anesthetized humans," *Anesthesiology*, vol. 59, no. 4, pp. 340–343, 1983.

[3] A. N. Hurewitz, U. Sidhu, E. H. Bergofsky, and A. D. Chanana, "How alterations in pleural pressure influence esophageal pressure," *Journal of Applied Physiology*, vol. 56, no. 5, pp. 1162–1169, 1984.

[4] M. E. B. Wohl, J. Turner, and J. Mead, "Static volume-pressure curves of dog lungs—in vivo and in vitro," *Journal of Applied Physiology*, vol. 24, no. 3, pp. 348–354, 1968.

[5] G. R. Washko, C. R. O'Donnell, and S. H. Loring, "Volume-related and volume-independent effects of posture on esophageal and transpulmonary pressures in healthy subjects," *Journal of Applied Physiology*, vol. 100, no. 3, pp. 753–758, 2006.

[6] J. Mead and E. A. Gaensler, "Esophageal and pleural pressures in man, upright and supine," *Journal of Applied Physiology*, vol. 14, no. 1, pp. 81–83, 1959.

[7] B. D. Higgs, P. K. Behrakis, D. R. Bevan, and J. Milic Emili, "Measurement of pleural pressure with esophageal balloon in anesthetized humans," *Anesthesiology*, vol. 59, no. 4, pp. 340–343, 1983.

[8] P. Pelosi, M. Goldner, A. McKibben et al., "Recruitment and derecruitment during acute respiratory failure: an experimental study," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 1, pp. 122–130, 2001.

[9] D. Talmor, T. Sarge, A. Malhotra et al., "Mechanical ventilation guided by esophageal pressure in acute lung injury," *The New England Journal of Medicine*, vol. 359, no. 20, pp. 2095–2104, 2008.

[10] D. Talmor, T. Sarge, C. R. O'Donnell et al., "Esophageal and transpulmonary pressures in acute respiratory failure," *Critical Care Medicine*, vol. 34, no. 5, pp. 1389–1394, 2006.

[11] C. G. Irvin, M. Sampson, L. Engel, and A. E. Grassino, "Effect of breathing pattern on esophageal pressure gradients in humans," *Journal of Applied Physiology*, vol. 57, no. 1, pp. 168–175, 1984.

[12] G. Dechman, J. Sato, and J. H. T. Bates, "Factors affecting the accuracy of esophageal balloon measurement of pleural pressure in dogs," *Journal of Applied Physiology*, vol. 72, no. 1, pp. 383–388, 1992.

[13] A. Baydur, P. K. Behrakis, W. A. Zin et al., "A simple method for assessing the validity of the esophageal balloon technique," *American Review of Respiratory Disease*, vol. 126, no. 5, pp. 788–791, 1982.

[14] M. A. Matthay, S. Bhattacharya, D. Gaver et al., "Ventilator-induced lung injury: in vivo and in vitro mechanisms," *American Journal of Physiology*, vol. 283, no. 4, pp. L678–L682, 2002.

[15] P. P. Terragni, G. L. Rosboch, A. Lisi, A. G. Viale, and V. M. Ranieri, "How respiratory system mechanics may help in minimising ventilator-induced lung injury in ARDS patients," *European Respiratory Journal Supplement*, vol. 42, pp. 15s–21s, 2003.

[16] T. Yoshida, A. Uchiyama, N. Matsuura, T. Mashimo, and Y. Fujino, "Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high

transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury," *Critical Care Medicine*, vol. 40, no. 5, pp. 1578–1585, 2012.

[17] S. Grasso, P. Terragni, A. Birocco et al., "ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure," *Intensive Care Medicine*, vol. 38, no. 3, pp. 395–403, 2012.

[18] C. L. Hodgson, D. V. Tuxen, A. R. Davies et al., "A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome," *Critical Care*, vol. 15, no. 3, article R133, 2011.

[19] K. K. Chung, S. E. Wolf, E. M. Renz et al., "High-frequency percussive ventilation and low tidal volume ventilation in burns: a randomized controlled trial," *Critical Care Medicine*, vol. 38, no. 10, pp. 1970–1977, 2010.

[20] A. Mekontso Dessap, C. Charron, J. Devaquet et al., "Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome," *Intensive Care Medicine*, vol. 35, no. 11, pp. 1850–1858, 2009.

[21] M. Badet, F. Bayle, J. C. Richard, and C. Guérin, "Comparison of optimal positive end-expiratory pressure and recruitment maneuvers during lung-protective mechanical ventilation in patients with acute lung injury/acute respiratory distress syndrome," *Respiratory Care*, vol. 54, no. 7, pp. 847–854, 2009.

[22] A. Mercat, J. C. M. Richard, B. Vielle et al., "Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial," *Journal of the American Medical Association*, vol. 299, no. 6, pp. 646–655, 2008.

[23] M. O. Meade, D. J. Cook, G. H. Guyatt et al., "Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial," *Journal of the American Medical Association*, vol. 299, no. 6, pp. 637–645, 2008.

[24] E. K. Wolthuis, G. Choi, M. C. Dessing et al., "Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury," *Anesthesiology*, vol. 108, no. 1, pp. 46–54, 2008.

[25] J. Pachl, K. Roubík, P. Waldauf, M. Fric, and V. Zábrodský, "Normocapnic high-frequency oscillatory ventilation affects differently extrapulmonary and pulmonary forms of acute respiratory distress syndrome in adults," *Physiological Research*, vol. 55, no. 1, pp. 15–24, 2006.

[26] K. E. A. Burns, N. K. J. Adhikari, A. S. Slutsky et al., "Pressure and volume limited ventilation for the ventilatory management of patients with acute lung injury: a systematic review and meta-analysis," *PLoS ONE*, vol. 6, no. 1, Article ID e14623, 2011.

[27] N. Petrucci and W. Iacovelli, "Lung protective ventilation strategy for the acute respiratory distress syndrome," *Cochrane Database of Systematic Reviews*, vol. 18, no. 3, p. CD003844, 2007.

[28] C. Putensen, N. Theuerkauf, J. Zinserling, H. Wrigge, and P. Pelosi, "Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury," *Annals of Internal Medicine*, vol. 151, no. 8, pp. 566–576, 2009.

[29] C. Hodgson, J. L. Keating, A. E. Holland et al., "Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation," *Cochrane Database of Systematic Reviews*, vol. 15, no. 2, p. CD006667, 2009.

[30] The Acute Respiratory Distress Syndrome Network, "Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome," *The New England Journal of Medicine*, vol. 342, no. 18, pp. 1301–1308, 2000.

[31] R. G. Brower, P. N. Lanken, N. MacIntyre et al., "Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome," *The New England Journal of Medicine*, vol. 351, no. 4, pp. 327–336, 2004.

[32] M. O. Meade, D. J. Cook, G. H. Guyatt et al., "Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial," *Journal of the American Medical Association*, vol. 299, no. 6, pp. 637–645, 2008.

[33] A. Mercat, J. C. M. Richard, B. Vielle et al., "Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial," *Journal of the American Medical Association*, vol. 299, no. 6, pp. 646–655, 2008.

[34] M. Briel, M. Meade, A. Mercat et al., "Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis," *Journal of the American Medical Association*, vol. 303, no. 9, pp. 865–873, 2010.

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 173527, 6 pages
doi:10.1155/2012/173527

Review Article

Failed Weaning from Mechanical Ventilation and Cardiac Dysfunction

Jahan Porhomayon,[1] Peter Papadakos,[2] and Nader D. Nader[3]

[1] *VA Western New York Healthcare System, Division of Critical Care Medicine, Department of Anesthesiology and Medicine, Buffalo School of Medicine and Biomedical Sciences, The State University of New York, Buffalo, NY 14215, USA*
[2] *Strong Memorial Hospital, University of Rochester, Rochester, NY 14642, USA*
[3] *VA Western New York Healthcare System, Division of Cardiothoracic Anesthesia and Pain Medicine, Department of Anesthesiology, Buffalo School of Medicine and Biomedical Sciences, The State University of New York, Buffalo, NY 14215, USA*

Correspondence should be addressed to Jahan Porhomayon, jahanpor@buffalo.edu

Received 20 June 2012; Accepted 3 August 2012

Academic Editor: Zsolt Molnar

Failure to transition patient from controlled mechanical ventilation to spontaneous breathing trials (SBTs) in a timely fashion is associated with significant morbidity and mortality in the intensive care unit. In addition, weaning failures are common in patients with limited cardiac reserves. Recent advances in cardiac echocardiography and laboratory measurement of serum biomarkers to assess hemodynamic response to SBT may provide additional information to guide clinicians to predict weaning outcome.

1. Introduction

Weaning critically ill patients from mechanical ventilation (MV) is a gradual and challenging process. Discontinuation of MV should be considered when patient is able to follow commands and maintain appropriate minute ventilation. In addition, protective airway reflexes should be intacts and patient clinical status must have improved. Clinical bedside assessment tools are crucial during the weaning trial (WT) so that ventilator requirements are met as the disease course is corrected. In April 2005, an international consensus conference sponsored by five major scientific societies was held in Budapest, Hungary to provide recommendations regarding the management of weaning process. The main recommendations were as follows: weaning should be considered as early as possible, patients should be divided to three categories (simple, difficult, prolonged weaning), a spontaneous breathing trial (SBT) is the major diagnostic test to determine whether patients can be successfully extubated, the initial trial should last 30 minutes and consist of either tracheal tube (T-Piece) breathing or low levels of pressure support, pressure support or assist-control ventilation modes should be favored in patients failing an initial trial/trials, and noninvasive ventilation techniques should be considered in selected patients to shorten the duration of intubation but should not be routinely used as a tool for extubation failure [1].

In general, mechanical weaning parameters are poor at predicting weaning success because they do not take into account cardiac reserves [2]. Therefore it is necessary for clinicians to understand the cardiovascular response to weaning trials and utilize the available tools to guide the wean team.

2. Physiology of Spontaneous Breathing Trials

MV weaning trial can be compared to a cardiac stress test where spontaneous ventilation is a form of an exercise [2], and therefore hemodynamic compromise can occur during weaning process in critically ill patients. The immediate transition from positive pressure mechanical ventilation to spontaneous ventilation may generate significant cardiopulmonary alterations based on the mode of weaning selected, particularly in individuals with preexisting cardiac dysfunction. Consideration of baseline cardiac reserve may be an important factor in the selection of an appropriate mode of spontaneous ventilation following controlled MV [3].

There are many studies reflecting on the concept of breathing as an exercise [4–8]. The important study by Mohsenifar et al. looked at the gastric intramural pH as a predictor of success or failure in weaning patients from mechanical ventilation. He concluded that gastrointestinal acidosis may be an early sign of weaning failure resulting from low cardiac output states [9]. The study by Jubran et al. looked at mixed venous oxygen saturation (SvO_2) monitoring for assessing hemodynamic performance and global tissue oxygenation in determining weaning outcome. He demonstrated that ventilator-supported patients who failed a trial of spontaneous breathing developed a progressive decrease in SvO_2 caused by the combination of a relative decrease in O_2 transport and an increase in O_2 extraction by the tissues [10].

The original study by Lemaire and colleagues looked at the hemodynamic effects of rapidly weaning patients from MV with severe chronic obstructive pulmonary disease (COPD) and cardiovascular disease who were recovering from acute cardiopulmonary decompensation. They showed that during spontaneous breathing trials on T-piece, majority of patients demonstrated marked increase in the pulmonary artery occlusion pressure, left ventricular end diastolic volume index, and controlled MV had to be resumed [11]. Similarly, Routsi et al. demonstrated that nitroglycerin infusion can expedite the weaning by restoring weaning-induced cardiovascular compromise in COPD patients [12]. The explanation for Lemaire finding is related to the changes in lung volumes.

It is important to recognize the physiologic effect of lung volumes and intrathoracic pressures (ITPs) on ventilation. Low lung volumes result in alveolar collapse and hypoxia, stimulating pulmonary vasomotor tone by the process of hypoxic pulmonary vasoconstriction [13]. In contrast, at high lung volumes the increase in pulmonary vascular resistance [14] and right ventricular afterload is largely due to increase in transpulmonary pressure [15] (Figure 1). Brower et al. and other investigators concluded that during spontaneous breathing trials (SBTs), hyperventilation can lead to increase in pulmonary vascular resistance [14], and patients with lung disease are more at risk for hyperinflation and hemodynamic changes [16, 17]. Pinsky also demonstrated that changes in lung volume alter autonomic tone and pulmonary vascular resistance (PVR), and high lung volumes compress the heart in the cardiac fossa. Hyperinflation increases PVR and pulmonary artery pressure, impeding right ventricular ejection fraction [18, 19].

Similarly, variations in intrathoracic pressure generated by different ventilator weaning modes may significantly affect hemodynamic and cardiovascular stability [20]. Heart is an intrathoracic organ; hence any changes in intrathoracic pressures (ITPs) can lead to changes in left ventricular (LV) afterload and venous return [21, 22]. In 1984, Pinsky elegantly demonstrated in his study that spontaneous inspiratory efforts decrease intrathoracic pressure (ITP). Decreases in ITP will augment venous return and impede LV ejection and increase intrathoracic blood volume. Since diaphragmatic descent increases intra-abdominal pressure, these combined effects cause decreased right atrial pressure and increased venous pressure in the abdomen, markedly

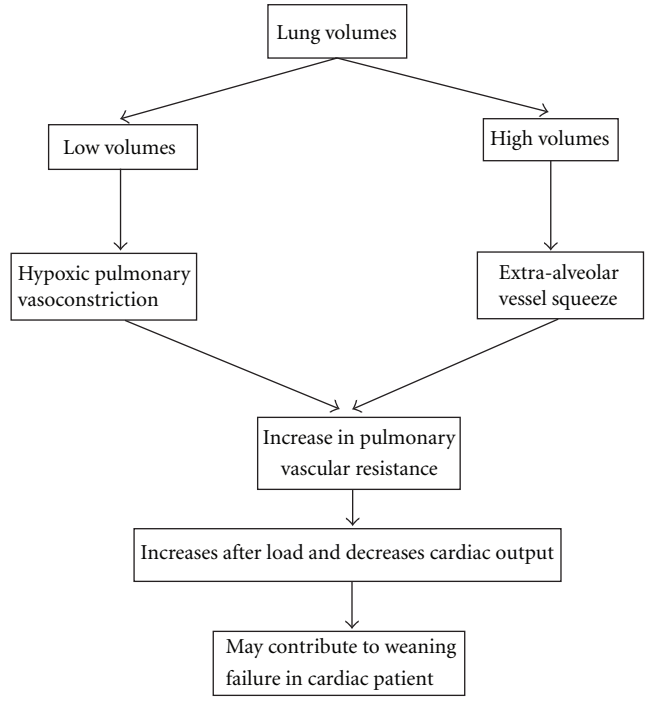


Figure 1

increasing the pressure gradient for systemic venous return [23]. Furthermore, the greater the decrease in ITP, the greater the increase in LV afterload for a constant arterial pressure, and right ventricle stroke output increases [24]. Pulmonary edema from negative pressure effect in patient breathing through the narrow endotracheal tube could also contribute to lower ITP.

It is now known that loaded spontaneous inspiration leads to increase in venous return and possible decompensation to heart failure or pulmonary edema [25–27]. Other investigators have similarly shown that increases in intrathoracic pressure increase right atrial pressure and decrease transmural LV systolic pressure. This will reduce the pressure gradients for venous return and LV ejection resulting in lower thoracic blood volume. This hemodynamic alteration generates a change in autonomic tone, so that cardiac output could be maintained. Therefore, individuals with autonomic and/or cardiovascular dysfunction may not be capable of this type of response and may fail to successfully wean from mechanical ventilation [20] (Figure 2).

3. Assessment of Cardiac Function during Weaning

3.1. B-Type Natriuretic Peptide. B-type natriuretic peptide levels are quantitative markers of cardiac stress and heart failure that summarize the degree of systolic and diastolic left ventricular dysfunction [28]. Initial observational pilot studies have addressed several potential indications in the intensive care unit: identification of cardiac dysfunction, diagnosis of hypoxic respiratory failure, risk stratification in severe sepsis and septic shock, evaluation of patients with shock [29],

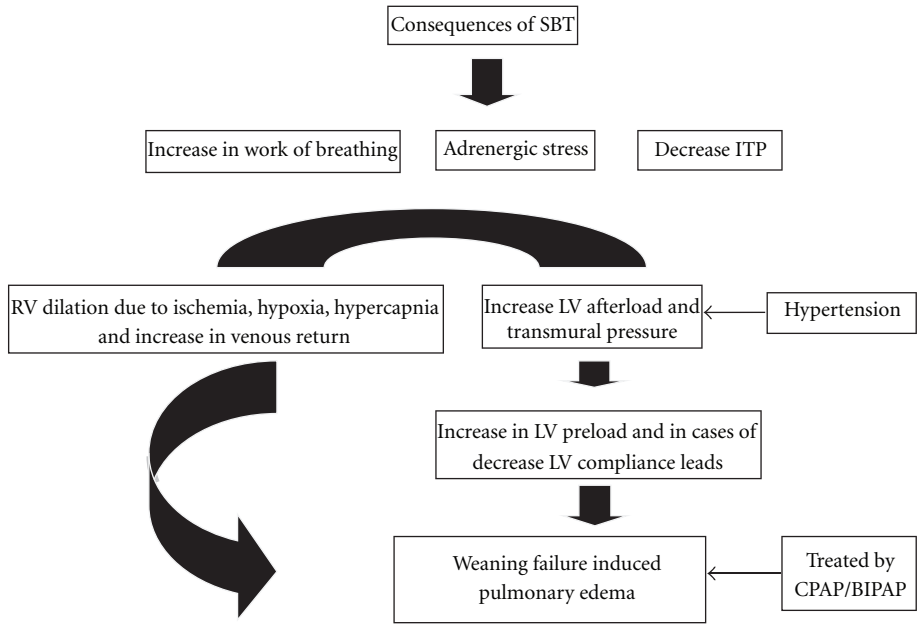


Figure 2: SBT: Spontaneous Breathing Trials, ITP: Intra-thoracic Pressure, CPAP: Continuous Positive Pressure Therapy, BIPAP: Bi-level Positive Pressure, LV: Left Ventricle, RV: Right Ventricle.

and weaning from mechanical ventilation [30]. B-type natriuretic peptide (BNP) is a cardiac neurohormone synthesized in the cardiac ventricles. It is released as a pre-pro-BNP peptide of 134 amino acids and is cleaved into pro-BNP (108 amino acids) and a signal peptide of 26 amino acids. Pro-BNP is subsequently cleaved into BNP (32 amino acids) and the inactive N-terminal pro-BNP peptide (NT-pro-BNP; 76 amino acids [Figure 3]) [31, 32]. The release of BNP into the circulation is directly proportional to the ventricular expansion and volume overload of the ventricles and therefore reflects the decompensated state of the ventricles [33, 34]. The effects of BNP—vasodilatation, natriuresis, and diuresis—lead to some improvement of the loading conditions of the failing heart.

Multiple studies have addressed the question of whether BNP or NT-pro-BNP could be used to identify patients who fail to wean for cardiac reasons [33–40]. The study by Zapata et al. was a prospective observational study of 100 MV patients [41]. All patients underwent spontaneous breathing trials over 48 hours and were assessed by transthoracic echocardiography, pulmonary artery catheter and BNP and NT-pro-BNP. They concluded that B-type natriuretic peptides, particularly BNP, can predict weaning failure due to heart failure (HF) before an SBT. Increases in natriuretic peptides during SBT are diagnostic of HF as the cause of weaning failure. BNP performs better than NT-pro-BNP in prediction and diagnosis of HF. The cut-off values using receiver operating (ROC) curve analyses to predict HF were 263 ng/L for BNP ($P < 0.001$) and 1,343 ng/L for NT-pro-BNP ($P = 0.08$). Mekontso-Dessap et al. [37] showed BNP levels after diuretic therapy were lower in patients with weaning success (517 pg/mL versus 226 pg/mL). Grasso et al. [40] used N-terminal pro-BNP to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. He showed that plasma levels of NT-pro-BNP increased significantly at the end of the spontaneous breathing trial only in patients with acute cardiac dysfunction (median 12,733, interquartile range 16,456 pg/mL, $P < 0.05$). Chien et al. [36] used the median BNP levels after the 2 hr SBT showing BNP levels were 461 (168–1202) pg/mL, 418 (218–1085) pg/mL, and 224 (112–660) pg/mL in the SBT failure, extubation failure, and extubation success groups, respectively. Gerbaud et al. [38] prospectively evaluated 44 patients with echocardiography and NT-pro-BNP. NT-pro-BNP levels (8199 (3106–10949) versus 4200 (1855–7125) pg/mL, $P = 0.004$) increased significantly in those who failed the SBT.

3.2. Echocardiography. There is growing indication to advocate that transthoracic echocardiography (TTE) should be used to categorize the cardiac origin of respiratory weaning failure. The study by Gerbaud et al. looks at the weaning trials in congestive heart failure patient by analysis of the mitral Doppler inflow E velocity to annular tissue Doppler E_a wave velocity (E/E_a) ratio measurement. Even though he concluded that TTE could not predict the outcome of SBT, he noticed cardiac index increased significantly at end-SBT in patients who passed [38]. In contrast, the study by Moschietto et al. in 68 patients on MV over 48 hours proved that measurement of the E/E_a ratio with TTE could predict weaning failure. Diastolic dysfunction with relaxation impairment was strongly associated with weaning failure. Additionally, the impossibility of enhancing the left ventricle relaxation rate during the SBT seemed to be the key factor of weaning failure. In contrast, the systolic dysfunction was not associated with weaning outcome [42]. Papanikolaou et al. evaluated 50 patients with Doppler echocardiography to predict outcome of weaning trials. The result indicated

Table 1: Prediction of respiratory weaning outcomes.

Author	Number	Study	Outcome
Zapata et al. [41]	100	Prospective	BNP or pro-BNP & ECHO predict WO
Gerbaud et al. [38]	44	Prospective	BNP or pro-BNP & ECHO did not predict WO
Papaioannou et al. [7]	42	Prospective	Cardiorespiratory dynamics predict WO
Chien et al. [36]	52	Prospective	Percent change of less than 20% in BNP predicts WO
Mekontso-Dessap et al. [37]	102	Prospective	Lower BNP levels before SBT may predicts WO
Moschietto et al. [42]	68	Prospective	ECHO predicts WO
Schifelbain et al. [44]	24	Prospective	ECHO did not predicts WO
Caille et al. [46]	117	Prospective	ECHO predicts WO
Grasso et al. [40]	19	Prospective	BNP predicts WO

ECHO: echocardiography, WO: weaning outcome, BNP: B-type natriuretic peptide.

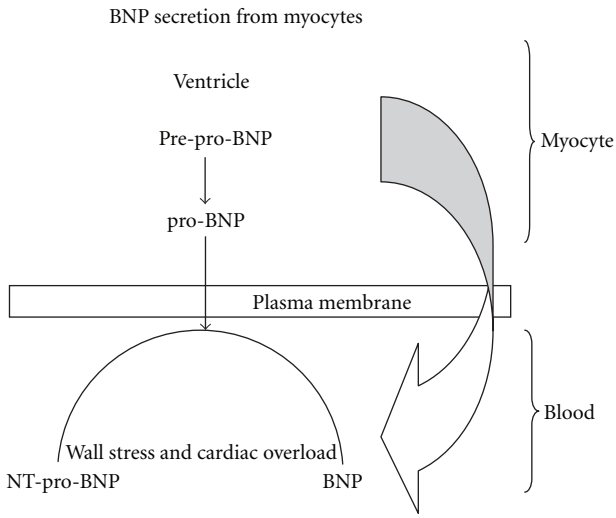


Figure 3: BNP: B-type natriuretic peptide, NT-pro-BNPL: N-terminal pro-B-type natriuretic peptide.

that LV diastolic dysfunction is significantly associated with weaning outcome in critically ill patients with preserved LV systolic function. An E/E_a ratio greater than 7.8 may identify patients at high risk of weaning failure [43]. Schifelbain et al. conducted randomized crossover clinical trial of 24 patients to analyze changes in cardiac function, using Doppler echocardiogram, in critical patients during weaning from MV. He used two different weaning methods: pressure support ventilation and T-tube. He did not find any differences between Doppler echocardiography and cardiorespiratory variables during pressure support ventilation and T-tube. However cardiac structures were smaller, isovolumetric relaxation time was larger, and oxygenation level was greater in successfully weaned patients [44]. It is probably safe to say that Doppler echocardiography has a place for assessment of weaning failure due to cardiac origin if performed routinely in the ICU. However, due to certain limitation relating to patient, it cannot be used in every patient [22, 45, 46] (Table 1).

3.3. Management of Weaning Failure from Cardiac Dysfunction. Therapeutic options should take into consideration the etiology of weaning failure. Weaning failure due to excessive preload should be treated with diuretic. It is important to rule out extra cardiac causes of weaning failure in such cases. Vasodilator therapy is indicated for weaning failure due to excessive afterload or myocardial ischemia. Additionally, alteration in ITP can be prevented by the use of CPAP/BIPAP (Figure 2). Noninvasive ventilation decreases cardiac stress load and should be utilized in weaning patients with poor cardiac reserves [47, 48]. In fact, positive pressure therapy is now the standard of care for treating patients with acute pulmonary edema and decreases afterload [3, 19]. Using the same physiological concept, Marino and Langhelle et al. and others have introduced the concept of resistive loaded breathing to augment cardiac output during cardiopulmonary resuscitation [49–52].

4. Conclusion

Assessment and prediction of weaning failure from cardiac origin remain complicated. Current prediction models are difficult to implement clinically at bedside. Echocardiography remains a valuable tool to monitor respiratory weaning process and requires expertise in image interpretation. Additionally, the need for multiple assessments makes it difficult to implement echocardiography as a routine monitor in the intensive care setting. Serum BNP and NT-pro-BNP appear promising to identify patients with heart failure during weaning process. However, laboratory turnover time and the accepted cut-off values for HF pose a clinical challenge for data interpretation in the intensive care arena.

5. Key Messages for Practicing Intensivists

(i) Ischemic heart disease, valvular heart disease, systolic or diastolic dysfunction contributes to increase in cardiac load and weaning failure.

(ii) Extra demand on cardiac working load imposed by SBT may become apparent when transferring patient from positive to spontaneous ventilation.

(iii) Diuretic therapy may be considered for excessive preload.

(iv) Noninvasive positive pressure ventilation is beneficial for weaning-induced pulmonary edema.

(v) Further cardiac evaluation is necessary if changes in natriuretic peptide levels are detected during SBT.

Conflict of Interests

Authors do not have any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

References

[1] J. M. Boles, J. Bion, A. Connors et al., "Weaning from mechanical ventilation," *European Respiratory Journal*, vol. 29, no. 5, pp. 1033–1056, 2007.

[2] M. R. Pinsky, "Breathing as exercise: the cardiovascular response to weaning from mechanical ventilation," *Intensive Care Medicine*, vol. 26, no. 9, pp. 1164–1166, 2000.

[3] S. K. Frazier, K. S. Stone, E. R. Schertel, D. K. Moser, and J. W. Pratt, "A comparison of hemodynamic changes during the transition from mechanical ventilation to T-piece, pressure support, and continuous positive airway pressure in canines," *Biological Research for Nursing*, vol. 1, no. 4, pp. 253–264, 2000.

[4] J. J. Kolkman, A. B. J. Groeneveld, F. G. Van Der Berg, J. A. Rauwerda, and S. G. M. Meuwissen, "Increased gastric pCO2 during exercise is indicative of gastric ischaemia: a tonometric study," *Gut*, vol. 44, no. 2, pp. 163–167, 1999.

[5] J. A. Otte, E. Oostveen, R. H. Geelkerken, A. B. J. Groeneveld, and J. J. Kolkman, "Exercise induces gastric ischemia in healthy volunteers: a tonometry study," *Journal of Applied Physiology*, vol. 91, no. 2, pp. 866–871, 2001.

[6] F. J. Hurtado, M. Berón, W. Olivera et al., "Gastric intramucosal pH and intraluminal PCO2 during weaning from mechanical ventilation," *Critical Care Medicine*, vol. 29, no. 1, pp. 70–76, 2001.

[7] V. E. Papaioannou, I. Chouvarda, N. Maglaveras, C. Dragoumanis, and I. Pneumatikos, "Changes of heart and respiratory rate dynamics during weaning from mechanical ventilation: a study of physiologic complexity in surgical critically ill patients," *Journal of Critical Care*, vol. 26, no. 3, pp. 262–272, 2011.

[8] B. Cabello, A. W. Thille, F. Roche-Campo, L. Brochard, F. J. Gómez, and J. Mancebo, "Physiological comparison of three spontaneous breathing trials in difficult-to-wean patients," *Intensive Care Medicine*, vol. 36, no. 7, pp. 1171–1179, 2010.

[9] Z. Mohsenifar, A. Hay, J. Hay, M. I. Lewis, and S. K. Koerner, "Gastric intramural pH as a predictor of success or failure in weaning patients from mechanical ventilation," *Annals of Internal Medicine*, vol. 119, no. 8, pp. 794–798, 1993.

[10] A. Jubran, M. Mathru, D. Dries, and M. J. Tobin, "Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof," *American Journal of Respiratory and Critical Care Medicine*, vol. 158, no. 6, pp. 1763–1769, 1998.

[11] F. Lemaire, J. L. Teboul, L. Cinotti et al., "Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation," *Anesthesiology*, vol. 69, no. 2, pp. 171–179, 1988.

[12] C. Routsi, I. Stanopoulos, E. Zakynthinos et al., "Nitroglycerin can facilitate weaning of difficult-to-wean chronic obstructive pulmonary disease patients: a prospective interventional non-randomized study," *Critical Care*, vol. 14, no. 6, article no. R204, 2010.

[13] T. S. Hakim, R. P. Michel, and H. K. Chang, "Effect of lung inflation on pulmonary vascular resistance by arterial and venous occlusion," *Journal of Applied Physiology*, vol. 53, no. 5, pp. 1110–1115, 1982.

[14] R. G. Brower, J. Gottlieb, and R. A. Wise, "Locus of hypoxic vasoconstriction in isolated ferret lungs," *Journal of Applied Physiology*, vol. 63, no. 1, pp. 58–65, 1987.

[15] J. B. Howell, S. Permutt, D. F. Proctor, and R. L. Riley, "Effect of inflation of the lung on different parts of pulmonary vascular bed," *Journal of Applied Physiology*, vol. 16, pp. 71–76, 1961.

[16] N. A. Bergman, "Properties of passive exhalations in anesthetized subjects," *Anesthesiology*, vol. 30, no. 4, pp. 378–387, 1969.

[17] C. M. Conway, "Haemodynamic effects of pulmonary ventilation," *British Journal of Anaesthesia*, vol. 47, no. 7, pp. 761–766, 1975.

[18] M. R. Pinsky, "Instantaneous venous return curves in an intact canine preparation," *Journal of Applied Physiology*, vol. 56, no. 3, pp. 765–771, 1984.

[19] M. R. Pinsky, "Cardiovascular issues in respiratory care," *Chest*, vol. 128, no. 5, supplement 2, pp. 592S–597S, 2005.

[20] S. K. Frazier, D. K. Moser, and K. S. Stone, "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," *Biological Research for Nursing*, vol. 2, no. 3, pp. 167–174, 2001.

[21] A. J. Buda, M. R. Pinsky, and N. B. Ingels, "Effect of intrathoracic pressure on left ventricular performance," *The New England Journal of Medicine*, vol. 301, no. 9, pp. 453–459, 1979.

[22] B. Lamia, J. Maizel, A. Ochagavia et al., "Echocardiographic diagnosis of pulmonary artery occlusion pressure elevation during weaning from mechanical ventilation," *Critical Care Medicine*, vol. 37, no. 5, pp. 1696–1701, 2009.

[23] M. R. Pinsky, "Determinants of pulmonary arterial flow variation during respiration," *Journal of Applied Physiology*, vol. 56, no. 5, pp. 1237–1245, 1984.

[24] R. A. Bronicki, M. Herrera, R. Mink et al., "Hemodynamics and cerebral oxygenation following repair of tetralogy of fallot: the effects of converting from positive pressure ventilation to spontaneous breathing," *Congenital Heart Disease*, vol. 5, no. 5, pp. 416–421, 2010.

[25] J. Yu, J. F. Zhang, A. M. Roberts, L. C. Collins, and E. C. Fletcher, "Pulmonary rapidly adapting receptor stimulation does not increase airway resistance in anesthetized rabbits," *American Journal of Respiratory and Critical Care Medicine*, vol. 160, no. 3, pp. 906–912, 1999.

[26] A. M. Miro, U. Shivaram, and P. J. P. Finch, "Noncardiogenic pulmonary edema following laser therapy of a tracheal neoplasm," *Chest*, vol. 96, no. 6, pp. 1430–1431, 1989.

[27] C. E. Oswalt, G. A. Gates, and F. M. G. Holmstrom, "Pulmonary edema as a complication of acute airway obstruction," *Journal of the American Medical Association*, vol. 238, no. 17, pp. 1833–1835, 1977.

[28] R. Berger, D. Moertl, S. Peter et al., "N-terminal pro-B-type natriuretic peptideg, intensive patient management in addition to multidisciplinary care in chronic heart failure. A 3-arm, prospective, randomized pilot study," *Journal of the American College of Cardiology*, vol. 55, no. 7, pp. 645–653, 2010.

[29] N. I. Nikolaou, C. Goritsas, M. Dede et al., "Brain natriuretic peptide increases in septic patients without severe sepsis or

shock," *European Journal of Internal Medicine*, vol. 18, no. 7, pp. 535–541, 2007.

[30] C. Mueller, A. Maisel, A. Mebazaa, and G. S. Filippatos, "The use of B-type natriuretic peptides in the intensive care unit," *Congestive Heart Failure*, vol. 14, no. 4, supplement 1, pp. 43–45, 2008.

[31] F. Boomsma and A. H. Van Den Meiracker, "Plasma A- and B-type natriuretic peptides: physiology, methodology and clinical use," *Cardiovascular Research*, vol. 51, no. 3, pp. 442–449, 2001.

[32] M. Kuhn, "Molecular physiology of natriuretic peptide signalling," *Basic Research in Cardiology*, vol. 99, no. 2, pp. 76–82, 2004.

[33] R. Pirracchio, R. Salem, and A. Mebazaa, "Use of B-type natriuretic peptide in critically ill patients," *Biomarkers in Medicine*, vol. 3, no. 5, pp. 541–547, 2009.

[34] T. Principi, G. Falzetti, D. Elisei, A. Donati, and P. Pelaia, "Behavior of B-type natriuretic peptide during mechanical ventilation and spontaneous breathing after extubation," *Minerva Anestesiologica*, vol. 75, no. 4, pp. 179–183, 2009.

[35] F. Abroug and L. Ouanes-Besbes, "Detection of acute heart failure in chronic obstructive pulmonary disease patients: role of B-type natriuretic peptide," *Current Opinion in Critical Care*, vol. 14, no. 3, pp. 340–347, 2008.

[36] J. Y. Chien, M. S. Lin, Y. C. T. Huang, Y. F. Chien, C. J. Yu, and P. C. Yang, "Changes in B-type natriuretic peptide improve weaning outcome predicted by spontaneous breathing trial," *Critical Care Medicine*, vol. 36, no. 5, pp. 1421–1426, 2008.

[37] A. Mekontso-Dessap, N. De Prost, E. Girou et al., "B-type natriuretic peptide and weaning from mechanical ventilation," *Intensive Care Medicine*, vol. 32, no. 10, pp. 1529–1536, 2006.

[38] E. Gerbaud, M. Erickson, M. Grenouillet-Delacre, M. C. Beauvieux, P. Coste, C. Durrieu-Jais et al., "Echocardiographic evaluation and N-terminal pro-brain natriuretic peptide measurement of patients hospitalized for heart failure during weaning from mechanical ventilation," *Minerva Anestesiol*, vol. 78, no. 4, pp. 415–425, 2012.

[39] A. Mekontso-Dessap, L. Tual, M. Kirsch et al., "B-type natriuretic peptide to assess haemodynamic status after cardiac surgery," *British Journal of Anaesthesia*, vol. 97, no. 6, pp. 777–782, 2006.

[40] S. Grasso, A. Leone, M. De et al., "Use of N-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease," *Critical Care Medicine*, vol. 35, no. 1, pp. 96–105, 2007.

[41] L. Zapata, P. Vera, A. Roglan, I. Gich, J. Ordonez-Llanos, and A. J. Betbesé, "B-type natriuretic peptides for prediction and diagnosis of weaning failure from cardiac origin," *Intensive Care Medicine*, vol. 37, no. 3, pp. 477–485, 2011.

[42] S. Moschietto, D. Doyen, L. Grech, J. Dellamonica, H. Hyvernat, and G. Bernardin, "Transthoracic echocardiography with doppler tissue imaging predicts weaning failure from mechanical ventilation: evolution of the left ventricle relaxation rate during a spontaneous breathing trial is the key factor in weaning outcome," *Critical Care*, vol. 16, no. 3, article R81, 2012.

[43] J. Papanikolaou, D. Makris, T. Saranteas, D. Karakitsos, E. Zintzaras, A. Karabinis et al., "New insights into weaning from mechanical ventilation: left ventricular diastolic dysfunction is a key player," *Intensive Care Medicine*. In press.

[44] L. M. Schifelbain, S. R. R. Vieira, J. S. Brauner, D. M. Pacheco, and A. A. Naujorks, "Echocardiographic evaluation during weaning from mechanical ventilation," *Clinics*, vol. 66, no. 1, pp. 107–111, 2011.

[45] G. Voga, "Hemodynamic changes during weaning: can we assess and predict cardiac-related weaning failure by transthoracic echocardiography?" *Critical Care*, vol. 14, no. 4, article no. 174, 2010.

[46] V. Caille, J. B. Amiel, C. Charron, G. Belliard, A. Vieillard-Baron, and P. Vignon, "Echocardiography: a help in the weaning process," *Critical Care*, vol. 14, no. 3, article no. R120, 2010.

[47] Y. Kaneko, J. S. Floras, K. Usui et al., "Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea," *The New England Journal of Medicine*, vol. 348, no. 13, pp. 1233–1241, 2003.

[48] M. Ferrer, A. Esquìnas, F. Arancibia et al., "Noninvasive ventilation during persistent weaning failure: a randomized controlled trial," *American Journal of Respiratory and Critical Care Medicine*, vol. 168, no. 1, pp. 70–76, 2003.

[49] A. Langhelle, T. Strømme, K. Sunde, L. Wik, G. Nicolaysen, and P. A. Steen, "Inspiratory impedance threshold valve during CPR," *Resuscitation*, vol. 52, no. 1, pp. 39–48, 2002.

[50] B. S. Marino, D. Yannopoulos, G. Sigurdsson et al., "Spontaneous breathing through an inspiratory impedance threshold device augments cardiac index and stroke volume index in a pediatric porcine model of hemorrhagic hypovolemia," *Critical Care Medicine*, vol. 32, no. 9, supplement, pp. S398–S405, 2004.

[51] T. P. Aufderheide, G. Nichol, T. D. Rea, S. P. Brown, B. G. Leroux, P. E. Pepe et al., "A trial of an impedance threshold device in out-of-hospital cardiac arrest," *The New England Journal of Medicine*, vol. 365, no. 9, pp. 798–806, 2011.

[52] K. G. Lurie, T. Zielinski, S. McKnite, T. Aufderheide, and W. Voelckel, "Use of an inspiratory impedance valve improves neurologically intact survival in a porcine model of ventricular fibrillation," *Circulation*, vol. 105, no. 1, pp. 124–129, 2002.

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 952168, 13 pages
doi:10.1155/2012/952168

Review Article

Goal-Oriented Respiratory Management for Critically Ill Patients with Acute Respiratory Distress Syndrome

Carmen Sílvia Valente Barbas,[1,2] Gustavo Faissol Janot Matos,[2] Marcelo Britto Passos Amato,[1] and Carlos Roberto Ribeiro Carvalho[1]

[1] *Respiratory ICU and LIM-09, Medical School, University of São Paulo, 6 Andar, Avenida Dr. Eneas de Carvalho Aguiar 155, 05403-000 São Paulo, SP, Brazil*
[2] *Adult ICU Albert Einstein Hospital, 5 Andar, Avenida Albert Einstein 627, 05652-900 São Paulo, SP, Brazil*

Correspondence should be addressed to Carmen Sílvia Valente Barbas, carmen.barbas@gmail.com

Received 2 June 2012; Accepted 19 July 2012

Academic Editor: Lars J. Bjertnaes

This paper, based on relevant literature articles and the authors' clinical experience, presents a goal-oriented respiratory management for critically ill patients with acute respiratory distress syndrome (ARDS) that can help improve clinicians' ability to care for these patients. Early recognition of ARDS modified risk factors and avoidance of aggravating factors during hospital stay such as nonprotective mechanical ventilation, multiple blood products transfusions, positive fluid balance, ventilator-associated pneumonia, and gastric aspiration can help decrease its incidence. An early extensive clinical, laboratory, and imaging evaluation of "at risk patients" allows a correct diagnosis of ARDS, assessment of comorbidities, and calculation of prognostic indices, so that a careful treatment can be planned. Rapid administration of antibiotics and resuscitative measures in case of sepsis and septic shock associated with protective ventilatory strategies and early short-term paralysis associated with differential ventilatory techniques (recruitment maneuvers with adequate positive end-expiratory pressure titration, prone position, and new extracorporeal membrane oxygenation techniques) in severe ARDS can help improve its prognosis. Revaluation of ARDS patients on the third day of evolution (Sequential Organ Failure Assessment (SOFA), biomarkers and response to infection therapy) allows changes in the initial treatment plans and can help decrease ARDS mortality.

1. Introduction

Acute respiratory distress syndrome (ARDS) is due to an increase in the pulmonary alveolar-capillary membrane permeability causing lung edema rich in protein and consequently acute hypoxemic respiratory failure in genetically susceptible patients exposed to determined risk factors [1–14]. A recent study showed that the del/del genotype (patients homozygous for the 4 base pair deletion in the promoter of NFKB1) is associated with an age-dependent increase in odds of developing ARDS (OR 5.21, 95% CI 1.35–20.0) and patients with the del/del genotype and ARDS also have increased hazard of 60-day mortality (HR 1.54, 95% CI 1.01–2.36) and more organ failure ($P < 0.001$) [15]. All age groups may be affected, although the syndrome has a higher incidence and mortality in older people [16]. The most common precipitating causes of ARDS are pulmonary infections, nonpulmonary sepsis, shock, gastric aspiration, thoracic trauma, fat embolism, near drowning, inhalational injury, cardiopulmonary bypass, drug overdose, acute pancreatitis, and high-risk trauma (especially traumatic brain injury) [17]. Recent epidemiological studies suggested a variety of intrahospital risk factors for ARDS development such as multiple blood products transfusions, mechanical ventilation with high tidal volumes, excessive fluid resuscitation, and hospital-acquired pneumonia as well as high-risk surgeries (especially aortic vascular, cardiac, and acute abdomen); all risk factors are potentially preventable. Chronic alcohol abuse, chronic liver disease, immunosuppression, hypoalbuminemia, and obesity are also all associated with the development of ARDS, whereas diabetes mellitus appears to be protective [17].

After exposure to a risk factor, there is an important activation of neutrophils and release of harmful mediators including cytokines (such as interleukins 1, 6, and 8 and soluble tumor necrosis factor-alpha receptors), proteases, reactive oxygen species, and matrix metalloproteinases leading to future damage. An overwhelming pulmonary inflammatory process is initiated leading to alveolar epithelial and vascular endothelial injury. Alveolar epithelial injury of type I cells contributes to the pulmonary edema and the breakdown of this epithelial barrier exposes the underlying basement membrane, predisposing to bacteremia and sepsis. Injury to type II alveolar cells leads to an impairment of surfactant function with consequent collapse of the lungs. Histopathologically there is diffuse alveolar damage with neutrophil infiltration, alveolar hemorrhage and hyaline membrane formation [18–22]. There are localized destruction and occlusion of the vascular bed of the lungs by intravascular thrombosis and an increment of the anatomical dead space resulting in an increase of arterial carbon dioxide associated with a poor outcome. Fibrosis can be evident histologically as early as one week after the onset of ARDS and procollagen III peptide, a precursor of collagen synthesis, can be elevated in bronchoalveolar lavage fluid of ARDS patients at the time of tracheal intubation, its increment being associated with a poor ARDS prognosis. Vascular injury and remodeling may lead to pulmonary arterial hypertension which may compromise right ventricular function associated with a poor clinical outcome [13].

2. Importance of Early Recognition of ARDS and Its Correct Diagnosis

Incorporation of modified risk factors such as acute increase of respiratory rate, presence of tachypnea, detection of pulse oximeter desaturation, increased necessity of oxygen supplementation, presence of low pH, acidosis, or hypoxemia in an arterial blood gas sample in clinical practice can improve the clinicians' ability to perform early diagnosis and prompt therapeutic intervention in ARDS [17]. The presence of these modified risk factors may alert physicians to avoid secondary hospital exposures, such as blood products transfusions, excessive fluid administration, infusion of potentially toxic drugs, high tidal volume mechanical ventilation, and gastric aspiration.

Implementation of ventilator associated pneumonia prevention bundles decreases the incidence of VAP and can lower the incidence of ARDS [17]. Implementation of automated ARDS electronic screening in USA hospitals such as "ASSIST" (electronic alert from laboratory when the arterial blood gas analysis shows hypoxemia and the radiology department when chest X-ray shows bilateral pulmonary infiltrates) to identify intubated patients with ARDS in medical and surgical ICUs showed a sensitivity of 97.6% (95% CI, 96.8–98.4%) and specificity of 96.8% (95% CI, 96.8–98.4%) when compared to a manual screening algorithm that had a sensitivity of 57.1% (95% CI, 54.5–59.8%) and specificity of 99.7% (95% CI, 99.4–100%) in 1270 ICU patients over a 21-week period during enrollment in ARDSNet trials [23]. The results of this study indicated the advantages of having an in-hospital automated screening of ARDS over manual screening. The automated screening can increase the chances of ARDS diagnosis, alert the clinicians, and elicit the rapid response from the hospital team of intensivists to initiate clinical protocols and ARDS therapeutic interventions [24].

Most hospitals and intensive care units worldwide use the standard criteria for the diagnosis of acute lung injury (ALI)/ARDS: presence of acute hypoxemia (PaO_2/FIO_2 less than 300 mmHg or 39.99 Kpa for ALI or less than 200 mmHg or 26.66 Kpa for ARDS), bilateral infiltrates seen on a frontal chest radiograph that are consistent with pulmonary edema, and no clinical evidence of left atrial hypertension, or (if it is measured) a pulmonary artery wedge pressure (PAWP) of less than 18 mmHg according to the 1994–1998 American-European Consensus Conference on ARDS (AECC) [25, 26]. This definition aimed to simplify and standardize the diagnosis of ARDS worldwide. However, in clinical practice, in order to detect and diagnose ALI/ARDS cases, physicians must focus on patients' complaints, physical examination alterations, patients at risk of developing the disease, or patients presenting finger pulse oximeter desaturation. Following the ALI/ARDS clinical suspicion, physicians should order an arterial blood gas analysis and a chest radiograph to be able to confirm the ALI/ARDS diagnosis. Recent updates of ARDS definition such as the 2005 Delphi consensus [8] or the Berlin definition [27] were published in order to improve ARDS diagnosis criteria. The Berlin definition reclassified ARDS as mild ($PaO_2/FIO_2 < 300$ or 39.99 Kpa), moderate ($PaO_2/FIO_2 < 200$ or 26.66 Kpa), and severe ($PaO_2/FIO_2 < 100$ mmHg or 13.33 Kpa) and removed the term ALI and the necessity of a Swan Ganz catheter to access PAWP. Acute time frame was specified as the onset within 1 week of a known clinical insult or new or worsening respiratory symptoms chest radiography criteria were clarified and bilateral opacities consistent with pulmonary edema were maintained as the main radiological criteria of ARDS, but it was recognized that these findings could be demonstrated on CT scan instead of chest radiograph. The recent Berlin definition of ARDS is a decisive step forward in refining the diagnosis of the syndrome, but PaO_2/FIO_2 is influenced by ventilator settings and this fact should be considered; bilateral pulmonary infiltrates can be the result of a wide variety of acute lung diseases that should be better investigated. Left and right ventricular function, pulmonary artery pressures, and volemic status could be better evaluated by bedside echocardiography and extravascular lung water can be measured using PiCCO catheter, in order to evaluate the degree of pulmonary edema. Predictors of mortality should be calculated at ICU admission. With the information, the ICU team can program a more careful treatment plan according to disease severity. The Berlin definition shows better predictive validity for mortality compared to the AECC definition, but the absolute value of the area under the receiver operating curve is still too small (0.577), suggesting that some factors are still missing. Further discussion and research are needed before we reach a comprehensive definition of ARDS.

3. Importance of Computer Tomography to the Diagnosis of ARDS, to Access the Severity of the Disease, to Make Differential Diagnoses, and to Set the ARDS Ventilatory Strategy

The typical findings of ARDS in a computer tomography reveal a heterogeneous bilateral pulmonary infiltrate predominantly in gravity-dependent regions of the lungs and more preserved lungs in nondependent lung regions. Using quantitative analysis of the CT scan, the gravity-dependent pulmonary ARDS infiltrate is typically nonaerated lung tissue consistent with compressive atelectasis [28, 29]. Lung weight assessed by CT scan is increased in ARDS and is correlated with the severity of the syndrome [27].

The finding of concomitant interstitial infiltrates suggests viral or mycoplasma, chlamydia or opportunistic pulmonary infections, or drug-induced lung disease.

The differential diagnosis of bilateral pneumonia, alveolar hemorrhage, and acute interstitial lung disease such as acute interstitial pneumonia, hypersensitivity pneumonitis, acute eosinophilic pneumonia, and bronchiolitis obliterans with organizing pneumonia can be suggested by the characteristic CT scan findings of each specific disease [12].

The results of stepwise lung recruitment maneuvers as well as positive end-expiratory (PEEP) titration to keep the lungs open with minimal collapse can be assessed by computer tomography analysis [30]. This strategy is aimed at opening up the lungs and keeping the lungs open [31] as quickly and early as possible as postulated by Lachmann [32] in order to have a huge improvement in lung function and avoid potential ventilator-induced lung injury. Recently, our group reported the experience with Maximal Recruitment Strategy (MRS) in 51 patients with ARDS. MRS consisted of 2-minute steps of tidal ventilation with pressure-controlled ventilation, fixed driving pressure of 15 cmH_2O, respiratory rate of 10 breaths/minute, inspiratory/expiratory ratio of 1 : 1, and stepwise increments in PEEP levels from 10 to 45 cmH_2O (recruitment phase). After that, PEEP was decreased to 25 cmH_2O and, then, from 25 to 10 cmH_2O (PEEP titration phase) in steps of 5 cmH_2O, each one lasting 4 minutes. At each of the steps computer tomography image sequences from the carina to the diaphragm were acquired during an expiratory pause of 6–10 seconds. Lung collapse was assessed online by visual inspection, for immediate clinical decision, and offline for quantitative measurements. MRS showed a statistically significant decrease in nonaerated areas of the ARDS lungs that was accompanied by a significant increment in oxygenation. The opening plateau pressure observed during the recruitment protocol was 59.6 ($\pm$5.9 cmH_2O), and the mean PEEP titrated after MRS was 24.6 ($\pm$2.9 cmH_2O). Mean PaO_2/FiO_2 ratio increased from 125 ($\pm$43) to 300 ($\pm$103; $P < 0.0001$) after MRS and was sustained above 300 throughout seven days. Nonaerated parenchyma decreased significantly from 53.6% (interquartile range (IQR): 42.5 to 62.4) to 12.7% (IQR: 4.9 to 24.2) ($P < 0.0001$) after MRS. The potentially recruitable lung was estimated at 45% (IQR: 25 to 53), (Figure 1). ICU mortality was 28% and hospital mortality was 32%. The independent risk factors associated with mortality were older age and higher driving pressures (or higher delta pressure control). There were no significant clinical complications with MRS or barotrauma [33]. A better evolution of these ARDS patients with less necessity of oxygen supplementation in the recovery phase of the disease and a better quality of life must be tested in prospective, controlled clinical trials. A recent meta-analysis showing beneficial effects on mortality using higher PEEP levels compared with lower PEEP in ARDS patients corroborates the results of our clinical case series of ARDS patients submitted to MRS [33].

ARDS is a biphasic disease that progresses from an acute exudative phase, characterized by epithelial and endothelial injury, neutrophilic aggregation, formation of hyaline membranes, alveolar edema, and hemorrhage, to an organizing phase, characterized by regeneration and healing via resolution or repair with persistent intra-alveolar and interstitial fibrosis [11]. It is crucial to make the diagnosis of ARDS in the acute phase (preferably less than 72 hours) in order to make it possible to open up the lungs with recruitment maneuvers and keep the lungs open with sufficient PEEP levels to enable a more homogenous ventilation, minimizing the possible ventilator-induced lung injury (VILI) triggers and allowing the recovery of the lungs [34–36]. A recent study analyzing 85 patients with ARDS graded into six findings according to the extent of fibroproliferation at the CT scan showed that higher CT scores were associated with statistically significant decreases in organ-failure free days as well as ventilator free days and were an independent risk factor for mortality (OR = 1.2, 95% CI 1.06–1.36, $P < 0.005$) [37].

4. Other Imaging Techniques to Evaluate the ARDS Lungs

Positron emission tomography with (^{18}F) fluorodeoxyglucose (FDG-PET) detects inflammatory cells and can assess lung inflammation in ARDS lungs helping in the understanding of ARDS physiopathology [38–40].

Lung ultrasonography is a new helpful tool that can be performed at bedside without radiation exposure. Thoracic ultrasound is widely used for diagnostic and therapeutic intervention in patients with pleural effusion and pneumothoraces. The assessment of lung recruitment and PEEP titration in ARDS patients at bedside using lung ultrasonography is a new promising technique [41]. Currently, the two main limitations of this technique are its inability to detect lung overdistension and its operator-dependent characteristic.

Thoracic electrical impedance tomography (EIT) is a highly promising imaging technique to apply at the bedside for PEEP titration in ARDS patients. New automated tools permit the calculation of the percentage of collapsed as well as overdistended lung tissue at decremental PEEP levels after lung recruitment maneuvers (Figure 3). The regional distribution of collapse and overdistension may provide insights about the lung pathology. This technique permits daily PEEP adjustments at the bedside and verification of tidal volume distribution, avoiding excessive end-expiratory collapse or tidal overdistention [42–45]. One of the main

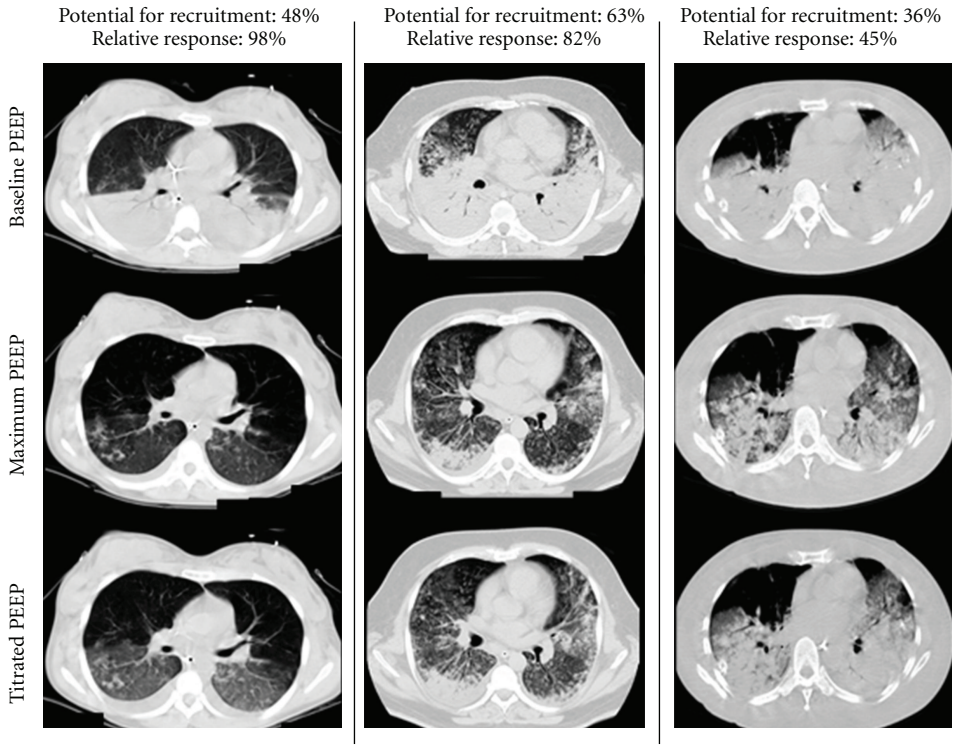


Figure 1: Computer tomographic evaluation of maximal recruitment strategy and adequate PEEP titration in early severe ARDS patients.

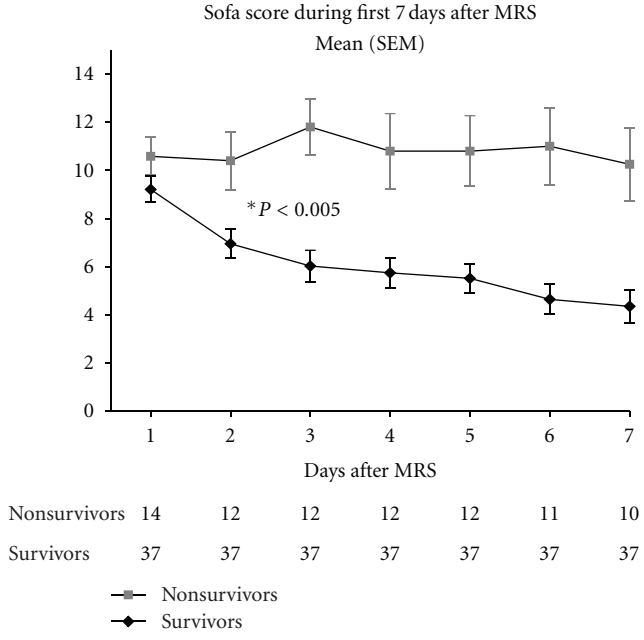


Figure 2: Sequential organ failure assessment (SOFA score) significantly decreases after the third day in ARDS survivors.

advantages of this technique is the possibility of around the clock monitoring. Further studies are needed to evaluate the clinical impact of these bedside techniques in ARDS patients' prognosis.

5. Importance of Noninvasive Ventilation in ARDS

Randomized trials suggested that patients with acute hypoxemic respiratory failure are less likely to require endotracheal intubation when noninvasive ventilation (NIV) is added to standard therapy [46]. However, most of these studies analyzed mixed causes of acute hypoxemic respiratory failure and reported the highest intubation rates for patients with ARDS (51 to 70%) and that the presence of ARDS was one factor independently associated with NIV failure and higher mortalities rates (50 to 70%). Recently, Zhan and colleagues [47] analyzed 40 patients with ARDS randomly allocated to receive either noninvasive ventilation or high-concentration oxygen therapy through a venturi mask. Noninvasive positive pressure ventilation decreased the respiratory rate and improved PaO_2/FIO_2 with time. The proportion of patients requiring intubation and invasive mechanical ventilation was significantly lower in the noninvasive ventilation group (one of 21 versus 7 of 19; $P = 0.02$). Therefore, noninvasive ventilation can be used as a first ventilatory support technique in selected patients with mild/moderate ARDS and a hemodynamic stable condition to avoid endotracheal intubation. A larger randomized trial, however, is required, with the need for intubation and mortality as the outcome of interest. A close-monitored initial trial of noninvasive ventilation should be considered in most mild/moderate ARDS patients, mainly the immunosuppressed ones with pulmonary infection in order to avoid intubation and invasive mechanical ventilation. However, early detection of

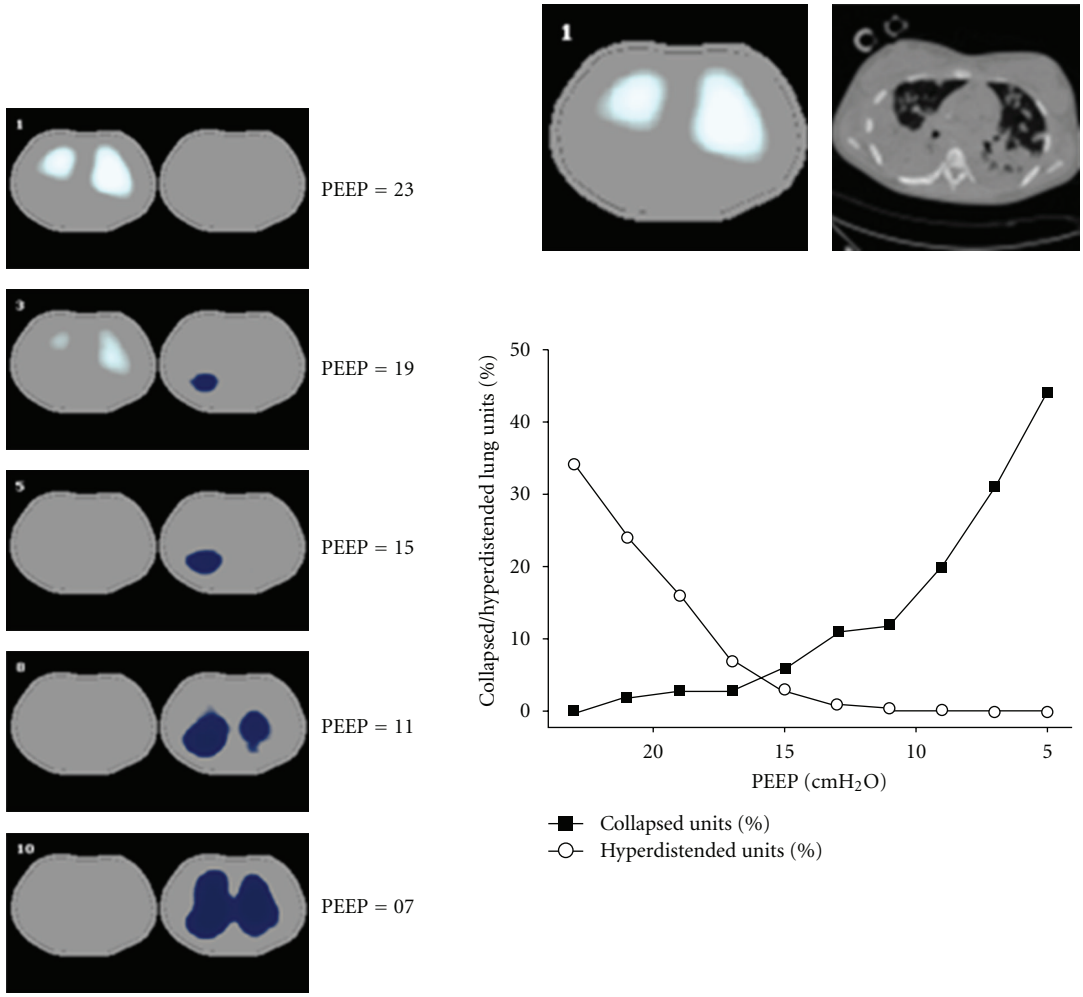


Figure 3: Peep titration with electrical impedance tomography in a patient with ARDS associated with H1N1-influenza virus infection. Legend: sequence of functional EIT images showing the progression of collapse along decremental PEEP levels (in blue, left panel) associated with progressive relief of overdistension (in white, left panel). Collapse was more prominent in the right lung. After analyzing the sequence of EIT images, the PEEP selected for this patient was 17 cmH_2O, believed to represent the best compromise between collapse and overdistension. According to the ARDSNet $PEEP/FIO_2$ table, this patient had been ventilated with a PEEP = 24 cmH_2O in the previous 48 hours. The patient was weaned from ventilator 3 days later.

NIV failure must be recognized, and a prompt intubation and mechanical ventilation must be provided in order to avoid complications.

6. Importance of Low Tidal Volume and Low Driving Pressure in ARDS

Protective ARDS mechanical ventilation strategies with tidal volumes equal to or less than 6 mL/Kg of predicted body weight have been traditionally associated with reduced mortality (when compared with 12 mL/Kg of predicted body weight) [48, 49]. A recent meta-analysis, however, scrutinized the specific role of various ventilatory strategies used in randomized trials on lung protection (like plateau-pressure limitation and higher PEEP use) and showed that tidal volume per se is not exactly the most important parameter to prioritize. The conclusion was that driving pressure (i.e., the difference between plateau pressure and PEEP during controlled mechanical ventilation) was the most important parameter to optimize at the bedside. Patients with high driving pressures (>16 cmH_2O) may be at great danger even when using tidal volumes below 6 mL/kg, or even when presenting plateau-pressures below 30 cmH_2O [50].

7. Importance of Static Pressure-Volume Curves of the Respiratory System to Set PEEP in ARDS

Amato and colleagues [51] demonstrated reduction in 28-day mortality in ARDS patients submitted to recruitment maneuver (CPAP 40 cmH_2O) PEEP titrated by static Pressure $\times$ Volume ($P \times V$) curve associated with low tidal volume (VT = 6 mL/kg), compared to those ventilated with high VT (12 mL/kg) and low PEEP strategy. It is hard to point

out which component of such combined strategy was responsible for the benefits. Villar and colleagues [52] found congruent results in a similar protocol. Moreover, Ranieri and colleagues [53] demonstrated decreased lung inflammation with this protective ventilatory strategy. Although these results are encouraging, the physiologic background supporting the use of *P-V* curves to titrate PEEP lacks consistency nowadays. In many different situations, investigators have reported a large dissociation between closing pressures of the lung and the calculated value for the inflection point obtained from the inspiratory *P-V* curve. In general, patients with high values of inflection point tend to have a more severe disease, and this may explain the relative success of this strategy. Nevertheless, we will probably use better tools to titrate PEEP in the next few years. A more consistent use of the *P-V* curve has been demonstrated for the analysis of lung recruitability [54, 55].

8. Importance of Assisted Ventilation in ARDS Patients: Airway-Pressure Release, BIPAP, Pressure Support Ventilation, and NAVA Ventilation

Airway pressure release ventilation is a modified form of continuous positive airway ventilation (CPAP) described by Stock and Dows in 1987 that uses fairly high prolonged CPAP levels with short and intermittent releases of the airway pressure to low CPAP levels allowing ventilation and CO_2 clearance. This mode of ventilatory support enhances oxygenation by augmenting alveolar recruitment and requires less sedation when used in ARDS patients compared to conventional mechanical ventilation [56, 57].

BiPAP ventilation combined with lung recruitment maneuvers can also be used in ARDS patients. Wang and colleagues compared this modality of ventilatory support with assist/controlled volume ventilation in a prospective, randomized trial of 28 ARDS patients showing a better PaO_2/FIO_2 ratio, pulmonary compliance, and a shorter duration of mechanical ventilation [58].

Pressure support ventilation (PSV) along with sufficient PEEP levels should be used as early as possible in ARDS patients to avoid respiratory muscle dystrophy and to decrease mechanical ventilation duration [32]. The reason for the improvement in oxygenation obtained with PSV in ARDS has been challenged in the recent years [59, 60]. The apparent improvement in recruitment seems to have been overstated and there is evidence that it is related to an increased perfusion of better ventilated lung areas, but not to decreased lung collapse. Growing concerns related to excessive tidal recruitment or excessive dyssynchrony during this mode of ventilation will have to be better addressed in the next years [61]. The advantages of using assist modes are to keep the respiratory muscles' activity, but sometimes it is difficult to synchronize the patients to the ventilators. Recently, neurally adjust ventilation (NAVA) was used in ARDS experimental models [62] and ARDS patients [63] demonstrating that the ventilation cycle and the magnitude of assist breath in NAVA matched the patients' breath pattern better than in PSV, NAVA improving patient-ventilator synchrony compared to PSV.

9. Importance of High Frequency Ventilation

High frequency oscillatory ventilation (HFOV) is an alternative mode of ventilatory support that can improve oxygenation by means of a higher mean airway pressure coupled with small tidal volumes generated by a piston pump oscillating at a frequency of 3–10 Hz and a higher respiratory rate. However, to date there are few studies involving a small number of patients comparing HFOV to conventional ventilation. A recent meta-analysis suggested a trend towards mortality benefit and more ventilator free days. However, the results of this analysis should be interpreted cautiously as the main study contributing to its results used high tidal volume in the control group rather than protective lung ventilation strategy [64].

10. Importance of Prone Position Ventilation

The use of the position change (supine to prone) leads to consistent improvement in arterial oxygenation in ARDS patients. Large randomized, controlled trials have consistently showed improvement in oxygenation without reduction in duration of mechanical ventilation or survival benefit. A recent meta-analyses suggest survival benefits in ARDS patients [65] or, more specifically, in a subgroup of patients with severe ARDS (PaO_2/FIO_2 < 100 mmHg) [66]. In our experience, the prone position can be an acceptable alternative to improve oxygenation in severe ARDS patients with arterial pulmonary hypertension and right ventricular dysfunction, which associated with the use of inhaled nitric oxide, can minimize intrathoracic pressures to facilitate right ventricular performance. The principles of a protective ventilation with proper PEEP titration and minimum driving pressures should also be pursued during prone positioning protocols.

11. Pulmonary Hypertension and Right Ventricular Dysfunction in ARDS Patients

Clinical studies suggested that elevated pulmonary artery systolic pressure in ARDS patients was associated with an adverse prognosis [67]. These data have been further supported by a more recent analysis of hemodynamic data from the ARDSNet Fluids and Catheter Therapy Trial (FACTT) [68]. The investigators assessed the transpulmonary gradient (TPG) (mean PA pressure-pulmonary capillary occlusion pressure (PCOP)) and the pulmonary vascular resistance index (PVRi) in a group of patients randomized to receive a pulmonary artery catheter to guide their ARDS management. Of note, all patients received a consistent protective ventilator strategy with target tidal volume ~6 mL/kg ideal body weight and plateau pressures maintained <30 cmH_2O. The highest recorded daily value of TPG and PVRi was used for the analysis. In the population of 475 patients randomized to receive a pulmonary artery catheter for ARDS

management, none of the baseline measures of cardiopulmonary dysfunction, including central venous pressure, PA systolic, or diastolic pressure, pulmonary capillary occlusion pressure (PAOP), or cardiac index distinguished survivors from nonsurvivors. In the pulmonary artery catheter population, 73% demonstrated an elevated transpulmonary gradient (TPG > 12). Patients with a TPG > 12 mmHg had a significantly greater mortality rate than patients with a TPG < 12 mmHg (30% versus 19%; $P = 0.02$). Patients with a persistently elevated TPG through day 7 of therapy had a significantly greater mortality than patients with an elevated TPG at day 0-1 which subsequently normalized. In multivariate analysis, pulmonary vascular dysfunction as represented by an elevated TPG and PVRi remained an independent predictor of an adverse outcome in the ARDS population. These data further support an important predictive role for pulmonary vascular disease in ARDS outcome [69]. In the largest published echocardiographic series of ARDS, 22% of patients receiving a consistent lung protective ventilation strategy (mean PEEP of 10 cmH_2O and mean plateau pressure (Pplat) of 23 cmH_2O) had evidence for acute cor pulmonale. In this population, 19% demonstrated evidence of a moderate-to-large patent foramen ovale [70]. The incidence of right to left shunting increased to 34% in patients with echocardiographic evidence of acute cor pulmonale.

12. Extracorporeal Membrane Oxygenation (ECMO) and Extracorporeal CO_2 Removal in ARDS

Increase of oxygenation and CO_2 removal by making the ARDS patients' blood pass throughout a membrane oxygenator outside the body is the principle of extracorporeal membrane oxygenation that can be applied venous-venous (good for oxygenation and CO_2 removal), arterial-venous (good for CO_2 removal), and venous-arterial (good for cardiovascular support). Early clinical trials of ECMO employed primarily an arterial-venous strategy with larger bore catheters for patients with intractable hypoxemia [71]. More modern investigations have used a safer venous-venous access approach [72, 73]. A recent UK prospective, randomized, clinical trial (CESAR) showed a survival advantage in the ECMO group (63% for ECMO versus 47% for controls). Nevertheless, the study was criticized as there was no standardized protocol management for the control group and some patients in the ECMO arm did not receive the proposed treatment [74]. The authors of CESAR trial also recommended transferring adult patients with severe but potentially reversible respiratory failure and a pH less than 7.20 on optimal conventional management, to a center with an ECMO-based management protocol to significantly improve survival without severe disability. The authors demonstrated that this strategy is also likely to be cost effective in settings with similar services to those in the United Kingdom [74]. Another recent approach for application of extracorporeal carbon dioxide removal new devices (ECMO-R) in ARDS patients is the demonstration that in severe ARDS even the low tidal volume ventilation with 6 mL/Kg of predicted body weight can cause tidal hyperdistension in the nondependent regions of the lungs accompanied by plateau airway pressures greater than 28 cmH_2O and elevated plasma markers of inflammation. In this group application of ECMO-R could allow the authors to decrease the tidal volume to less than 6 mL/kg with a consequent plateau pressure less than 25 cmH_2O that was associated with a lower radiographic index of lung injury and lower levels of lung-derived inflammatory cytokines. However, prognostic implication of this new ECMO-R devices application in clinical practice is still under investigation [75].

Pumpless interventional lung assist (iLA) is also used in patients with ARDS and is aimed at improving extracorporeal gas exchange with a membrane integrated in a passive arteriovenous shunt. iLA serves as an extracorporeal assist to support mechanical ventilation by enabling low tidal volume and a reduced inspiratory plateau pressure in extremely severe ARDS patients. Zimmermann and colleagues used iLA in 51 severe ARDS patients and observed a decrease in $PaCO_2$ allowing the decrease in tidal volume and plateau pressure (ultraprotective ventilation) with a hospital mortality rate of 49% [76].

13. Combining Ventilatory Support Therapies in ARDS Patients

Some authors suggest the use of combined ventilatory strategies in patients with ARDS. Bingold and colleagues [77] successfully used superimposed high-frequency jet ventilation (SHFJV) in combination with continuous positive airway pressure/assisted spontaneous breathing (CPAP/ASB) in five patients with H1-N1-associated ARDS to improve oxygenation. Varpula and colleagues [78] demonstrated a significant improvement in oxygenation in 28 ARDS patients, when they compared APVR associated with prone ventilation to SIMV-Pressure control/pressure support group. APRV after 24 h appears to enhance improvement in oxygenation in response to prone positioning. Rival and colleagues [79] examined the effects of the prone position associated with a recruitment maneuver consisting of 45 cmH_2O extended sigh in pressure control, in 16 ARDS patients. The combination of both ventilatory techniques led to the highest increase in PaO_2/FIO_2 ratio without significant clinical side effects. Lubnow and colleagues [80] examined the effects of 6 days of the combination of high-frequency oscillatory ventilation (HFOV) and extracorporeal carbon dioxide removal with the interventional lung assist (iLA) in 21 severe ARDS patients who failed conventional ventilation. They observed an increase in PaO_2/FIO_2 ratio and pH and a decrease in $PaCO_2$. Weaning from HFOV/iLA was successful in 10 patients. The 30-day mortality rate was 43%, and hospital mortality rate was 57%.

In conclusion, combined ventilatory strategies can be applied in severe ARDS patients, but the best match among all the available ventilatory techniques is still a matter of debate.

14. Importance of Early Detection and Treatment of Infection/Inflammation Associated with ARDS

Pulmonary infection and sepsis are the most important triggering factors of ARDS. Pulmonary infection has been associated with a higher risk of ARDS progression in comparison to nonpulmonary infection in at risk populations [81]. A wide variety of organisms can invade the respiratory tract and trigger host innate and acquired immune system initiating the inflammatory cascade of ARDS, sepsis, and multiple organ failure [11]. It is particularly pertinent to investigate the etiology of pulmonary infection on the first day assessing a nasal swab for a respiratory virus detection (Influenza, adenovirus) lower respiratory tract secretion or a bronchoalveolar lavage fluid (BALF) for bacteria (especially multiresistant species), other viruses as herpes and cytomegalovirus, coronavirus, or metapneumonic virus [82]. Opportunistic agents such as Pneumocystis jiroveci must be investigated in immunosuppressed patients. Urinary screening for Legionella species is decisive, because if positive, specific therapy must be introduced [11]. The assessment of BALF on the first as well as on the third day of mechanical ventilation is of the utmost importance not only in terms of assessment of etiology of pulmonary infection but also of the assessment of proinflammatory mediators of ARDS (IL-1, IL6, IL8, IL 10, soluble tumor necrosis factor-alpha receptors (sTNFR), and soluble intercellular adhesion molecule-1) and mediators of ventilator-induced lung injury (that can also be obtained in the plasma) such as sTNFR, IL6, IL8, and IL-10, indicators of epithelial cell injury (soluble advanced glycation end-product receptors-sRAGE), and surfactant protein-D, components of the coagulation system (protein-C and plasminogen activator inhibitor 1) [11, 83]. Elevated levels of procollagen peptide III in lavage fluid from patients on day 3 of ARDS were independent risk factors for mortality [84].

Procalcitonin (PCT) and C-reactive protein (CRP) are progressively being used in critical care setting in order to diagnose pulmonary infection and sepsis and to guide the antibiotic therapy. Procalcitonin levels correlated with severe sepsis and bacteraemia [85]. A PCT-based algorithm guiding initiation and duration of antibiotic therapy in critical ill patients with suspected bacterial infections was associated with a 23% relative reduction in antibiotic exposure with no significant increase in mortality [86]. The persistence of an elevated serum CRP in critical ill patients with ARDS may alert the intensivist to a possible persistent infection or inflammatory process. At this moment, a new workup for infection and change in antibiotic therapy could help improve the patient's evolution. Early and quick administration of antibiotics in sepsis and septic shock as well as early goal resuscitative measures for septic shock or early goal-directed therapy decrease mortality in this high mortality critically ill conditions [87, 88].

We also suggest that preventive measures to avoid gastric aspiration (elevated decubitus, intermittent check for residual gastric content during diet infusion) and to avoid ventilation associated pneumonia (wash hands, elevated decubitus, special endotracheal tubes) should be implemented.

15. Resolution of ARDS

The resolution of pulmonary edema is central to recover from ALI as it entails regression of air space inflammation and restoration of a functioning alveolar-capillary membrane. Accordingly, elevated extravascular lung water measured using this technique early in the course of ALI/ARDS, particularly if indexed to predicted body weight, was associated with a poor prognosis [89].

16. Importance of Early Diagnosis, Evaluation, and Treatment of Multiple Organ Failure Associated with ARDS

A study analyzing the evolution of ARDS patients showed that unknown-site infection (adjusted hazard ratio (HR) 3.08, 95% CI 1.37–6.90) and multiple site infection (adjusted HR 1.63, 95% CI 1.13–2.35) were associated with increased mortality [90]. In ARDS patients it is of considerable significance to evaluate the source of infection as well all organs and systems affected by the sepsis syndrome in order to map the organism (number of nonpulmonary organ failures), to calculate the prognostic indices (Acute Physiology and Chronic Health Evaluation (APACHE) and Simplified Acute Physiology Score (SAPS)) and to plan the multiorgan system approach to treat the disease. The higher the number of multiple organ failure associated with ARDS, the higher the hospital mortality. Trauma patients with ARDS are associated with lower mortality and oliguricrenal failure, while septic shock patients are associated with the highest hospital mortality rates, suggesting that during the first day of hospitalization these ARDS patients should be stratified and treated according to the severity of the syndrome and associated comorbidities [91]. In our case series of 51 patients with early severe ARDS the mean APACHE II score was 20.2 ± 6.2 (predicted mortality of 40%), median SOFA score (day 1) was 10 (7 to 12), median nonpulmonary organ failure was 2 (1 to 2), sepsis was present in 71% of our patients, and septic shock in 63%, vasopressors were used in 82.3% of our patients, and continuous renal replacement therapy was used in 56.8% of our patients. APACHE II and day 1 SOFA score were not associated with hospital mortality, but day 3 SOFA score was [33] (Figure 2) showing that a revaluation of the ARDS patients especially the ones with multiple organ failure and maintenance of SOFA score higher than 8 at day 3 has to be considered in order to evaluate hidden sources of infection or to change the antibiotics according to day 1 collected cultures.

17. Early Short-Term Paralysis in Severe ARDS Patients

In moderate-severe ARDS patients ($PaO_2/FIO_2 < 150$), a phase IV randomized controlled trial comparing cisatracurium to placebo for 48 hours showed an improved

adjusted 90-day survival rate and increased ventilator-free in the cisatracurium group without a significant increase in muscle weakness. Short-term paralysis may facilitate patient-ventilator synchrony in the setting of lung protective ventilation. Short-term paralysis would eliminate patient triggering and expiratory muscle activity. In combination, these effects may serve to limit regional overdistention and cyclic alveolar collapse. Paralysis may also act to lower metabolism and overall ventilatory demand [92].

18. Importance of Other Pharmacological Therapies in ARDS Patients

Inhaled nitric oxide is an endogenous vasodilator that reduces V/Q mismatch and improves oxygenation by pulmonary vasodilation in alveolar units that are ventilated, reducing pulmonary vascular resistance in patients with ARDS. A Cochrane review of 14 clinical trials with 1303 patients showed only a transient improvement in oxygenation with no benefit regarding length of ICU or hospital stay, ventilator-free days or survival. An increased renal impairment was observed in the inhaled nitric oxide-treated group [93].

The effects of steroids in the late-stage fibrotic phase of ARDS (after 7 days of onset) were tested in a phase III study of the ARDS network. The study showed no mortality benefit in the treatment group, with a higher mortality in patients treated 14 days after onset [94]. Recently, Seam and colleagues tested the effects of methylprednisolone infusion in 55 early ARDS patients compared to placebo. They observed that methylprednisolone therapy was associated with greater improvement in lung injury score ($P = 0.003$), shorter duration of mechanical ventilation ($P = 0.005$), and lower intensive care unit mortality ($P = 0.05$) than in the control subjects. On days 3 and 7, methylprednisolone decreased interleukin-6 and increased protein-C levels ($P < 0.001$) compared with control subjects [95]. From the available evidence, low-dose steroids (1-2 mg/Kg/methylprednisolone) may be considered in patients with severe early ARDS. Nevertheless, it is not recommended to initiate corticosteroids beyond 14 days after the onset of ARDS.

Ketoconazole, lisofylline, sivelestat, N-acetylcysteine, and exogenous surfactant are not recommended as treatment for ARDS patients [12].

19. Importance of Fluid Management and Alveolar Fluid Clearance in ARDS Patients

Cumulative positive fluid balance is associated with worse clinical outcomes in patients with ARDS. A phase III study conducted by the ARDS network (the FACTT study) compared liberal versus conservative fluid strategy in patients with acute lung injury. They observed an improvement in oxygenation, lung injury score (LIS), and shortened duration of mechanical ventilation without any increase in other organ failure in the conservative group, despite no difference in hospital mortality [68].

Beta-agonists were investigated in multicenter, prospective, randomized trials in their aerosolized presentation (the ALTA study) and their intravenous presentation (the BALTI-2 study). Both studies showed no mortality benefit and Beta-agonists are not recommended as part of therapy for patients with ARDS [96].

20. Importance of Nutrition in ARDS Patients

The OMEGA study [97], a randomized, double-blind, placebo-controlled, multicenter trial analyzed 272 patients with early acute lung injury allocated to receive either twice-daily enteral supplementation of n-3 fatty acids, γ-linolenic acid, and antioxidants compared with an isocaloric control. Enteral nutrition, directed by a protocol, was delivered separately from the study supplement. The patients that received enteral supplementation had fewer ventilator-free days (14 versus 17.2, $P = 0.02$), more days with diarrhea (29 versus 21%; $P = 0.001$), and no difference in the adjusted 60-day mortality (25.1% versus 17.6%; $P = 0.11$). More recently, a randomized, open-label, multicenter trial, the Eden study [98], reported 1000 patients with acute lung injury, randomized to receive either trophic or full enteral feeding for the first 6 days. Initial trophic enteral feeding did not improve ventilator-free days, 60-day mortality, or infection complications but was associated with less gastrointestinal intolerance.

Finally, based on relevant literature articles and the authors' clinical experience, we suggest a goal-oriented management for critically ill patients with ARDS that can help improve clinicians' ability to care for these patients (as shown below).

Algorithm for Goal-Oriented Management for Critically Ill Patients with ARDS. Correct ARDS Diagnosis. Acute onset, increase respiratory rate, pulse oximeter desaturation and hypoxemia ($PaO_2/FIO_2 < 300$).

Exposure to Traditional or Modified Risk Factors. Chest X-Ray Bilateral Pulmonary Infiltrates.

(i) If possible, get a computer tomography (improved diagnosis accuracy, permits differential diagnoses, and helps to set recruitment maneuvers and adequate PEEP levels).

(ii) Lung ultrasound, FDG-PET CT, electrical impedance tomography, and pressure-volume $P \times V$ curves can help assess the correct diagnosis and set protective mechanical ventilation.

(iii) Get nasal swab and inferior respiratory tract secretion for infection diagnosis or a BAL (infection diagnosis and proinflammatory mediators and procollagen III measurements).

(iv) Get hemocultures and blood for infection detection. Start resuscitative measurements for septic shock and start appropriate antibiotics.

(v) Assessment of prognostic indices (APACHE, SAPS) and sequential organ failure assessment (SOFA) score.

Standardize Initial Mechanical Ventilation for Blood Gas Measurements. Tidal volume: 6 mL/Kg predicted body weight, PEEP of 5 cmH_2O, RR = 20.

Classify ARDS Severity. Mild: $PaO_2/FIO_2 < 300$, moderate: $PaO_2/FIO_2 < 200$, and severe: $PaO_2/FIO_2 < 100$.

(i) If possible, get a Doppler echocardiogram to assess left ventricular function, right ventricular function, systolic pulmonary artery pressure, and vena cava compressibility.

(ii) Measure extravascular lung water, if available.

(a) In cases of severe ARDS consider recruitment maneuvers and adequate PEEP titration.

(b) In cases of severe ARDS with right ventricular dysfunction and pulmonary artery hypertension consider prone position and inhaled nitric oxide.

(c) In cases of excessive CO_2 retention: $PaCO_2 > 80$ mmHg and pH < 7.2 consider intratracheal gas insufflation and extracorporeal CO_2 removal.

21. Conclusions

(i) Early recognition of ARDS modified risk factors and avoidance of aggravating factors during hospital stay such as high tidal volume ventilation, multiple blood products transfusions, excessive fluid administration, ventilator associated pneumonia, and gastric aspiration prevention could help decrease its incidence.

(ii) An early extensive clinical, laboratory, and imaging evaluation of "at risk patients" allows a correct diagnosis of ARDS, assessment of comorbidities, calculation of prognostic indices (APACHE, SAPS, SOFA), stratification of the severity of ARDS, and planning a careful treatment.

(iii) Rapid administration of antibiotics and resuscitative measures in case of sepsis and septic shock associated with protective ventilatory strategies and early short-term paralysis associated with differential ventilatory techniques (recruitment maneuvers with adequate PEEP titration, prone position, and new ECMO techniques) in severe ARDS can help improve its prognosis.

(iv) Revaluation of ARDS patients on the third day of evolution (SOFA, biomarkers, and response to infection therapy) allows changes in the initial treatment plans and can help decrease ARDS mortality.

(v) Fibroproliferative changes on high-resolution CT in ARDS can predict mortality and ventilator dependency.

Acknowledgment

The authors would like to thank Adriana Pardini for revision of the language.

References

[1] D. G. Ashbaugh, D. B. Bigelow, T. L. Petty, and B. E. Levine, "Acute respiratory distress in adults," *Lancet*, vol. 2, no. 7511, pp. 319–323, 1967.

[2] J. F. Murray, M. A. Matthay, J. M. Luce, and M. R. Flick, "An expanded definition of the adult respiratory distress syndrome," *American Review of Respiratory Disease*, vol. 138, no. 3, pp. 720–723, 1988.

[3] L. B. Ware and M. A. Matthay, "The acute respiratory distress syndrome," *New England Journal of Medicine*, vol. 342, no. 18, pp. 1334–1349, 2000.

[4] A. Esteban, P. Fernández-Segoviano, F. Frutos-Vivar et al., "Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings," *Annals of Internal Medicine*, vol. 141, no. 6, pp. 440–445, 2004.

[5] C. R. Bernard, "Acute respiratory distress syndrome: a historical perspective," *American Journal of Respiratory and Critical Care Medicine*, vol. 172, no. 7, pp. 798–806, 2005.

[6] N. D. Ferguson, F. Frutos-Vivar, A. Esteban et al., "Acute respiratory distress syndrome: underrecognition by clinicians and diagnostic accuracy of three clinical definitions," *Critical Care Medicine*, vol. 33, no. 10, pp. 2228–2234, 2005.

[7] L. B. Ware and M. A. Matthay, "Acute pulmonary edema," *New England Journal of Medicine*, vol. 353, no. 26, pp. 2788–2796, 2005.

[8] N. D. Ferguson, A. M. Davis, A. S. Slutsky, and T. E. Stewart, "Development of a clinical definition for acute respiratory distress syndrome using the Delphi technique," *Journal of Critical Care*, vol. 20, no. 2, pp. 147–154, 2005.

[9] A. P. Wheeler and G. R. Bernard, "Acute lung injury and the acute respiratory distress syndrome: a clinical review," *Lancet*, vol. 369, no. 9572, pp. 1553–1564, 2007.

[10] C. S. V. Barbas, "Acute lung injury and acute respiratory distress syndrome: diagnostic hurdles," *Jornal Brasileiro de Pneumologia*, vol. 33, no. 4, pp. 25–26, 2007.

[11] L. Su, R. Zhai, C. C. Sheu et al., "Genetic variants in the angiopoietin-2 gene are associated with increased risk of ARDS," *Intensive Care Medicine*, vol. 35, no. 6, pp. 1024–1030, 2009.

[12] A. Dushianthan, M. P. W. Grocott, A. D. Postle, and R. Cusack, "Acute respiratory distress syndrome and acute lung injury," *Postgraduate Medical Journal*, vol. 87, pp. 612–622, 2011.

[13] M. Donahoe, "Acute respiratory distress syndrome: a clinical review," *Pulmonary Circulation*, vol. 1, no. 2, pp. 192–211, 2011.

[14] C. Pierrakos, M. Karanikolas, S. Scolletta, V. Karamouzos, and D. Velissaris, "Acute respiratory distress syndrome: pathophysiology and therapeutic options," *Journal of Clinical Medicine and Research*, vol. 4, no. 1, pp. 7–16, 2012.

[15] E. K. Bajwa, P. C. Cremer, M. N. Gong et al., "An NFKB1 promoter insertion/deletion polymorphism influences risk and outcome in acute respiratory distress syndrome among caucasians," *PLoS One*, vol. 6, no. 5, Article ID e19469, 2011.

[16] G. D. Rubenfeld, E. Caldwell, E. Peabody et al., "Incidence and outcomes of acute lung injury," *New England Journal of Medicine*, vol. 353, no. 16, pp. 1685–1693, 2005.

[17] O. Gajic, O. Dabbagh, P. K. Park et al., "Early identification of patients at risk of acute lung injury: evaluation of lung injury

prediction score in a multicenter cohort study," *American Journal of Respiratory and Critical Care Medicine*, vol. 183, no. 4, pp. 462–470, 2011.

[18] B. Corrin, "Diffuse alveolar damage, the pathological basis of adult respiratory distress syndrome," in *Pathology of the Lung*, B. Corrin, Ed., pp. 121–143, Churchill Livingstone, London, UK, 2000.

[19] Y. Fukuda, M. Ishizaki, Y. Masuda, G. Kimura, O. Kawanami, and Y. Masugi, "The role of intra-alveolar fibrosis in the process of pulmonary structural remodeling in patients with diffuse alveolar damage," in *The American Journal of Pathology*, vol. 126, pp. 171–182, 1987.

[20] C. A. Piantadosi and D. A. Schwartz, "The acute respiratory distress syndrome," *Annals of Internal Medicine*, vol. 141, no. 6, pp. 460–470, 2004.

[21] C. Y. Castro, "ARDS and diffuse alveolar damage: a pathologist's perspective," *Seminars in Thoracic and Cardiovascular Surgery*, vol. 18, no. 1, pp. 13–19, 2006.

[22] L. B. Ware, "Clinical year in review III: asthma, lung transplantation, cystic fibrosis, acute respiratory distress syndrome," *Proceedings of the American Thoracic Society*, vol. 4, no. 6, pp. 489–493, 2007.

[23] H. C. Koenig, B. B. Finkel, S. S. Khalsa et al., "Performance of an automated electronic acute lung injury screening system in intensive care unit patients," *Critical Care Medicine*, vol. 39, no. 1, pp. 98–104, 2011.

[24] C. S. V. Barbas, "Introducing automated acute lung injury/acute respiratory distress syndrome electronic screening in intensive care unit practice: is it the future?" *Critical Care Medicine*, vol. 39, no. 1, pp. 209–210, 2011.

[25] G. R. Bernard, A. Artigas, K. L. Brigham et al., "The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination," *American Journal of Respiratory and Critical Care Medicine*, vol. 149, no. 3 I, pp. 818–824, 1994.

[26] A. Artigas, G. R. Bernard, J. Carlet et al., "The American-European consensus conference on ARDS, part 2: ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling. Acute respiratory distress syndrome," *American Journal of Respiratory and Critical Care Medicine*, vol. 157, no. 4, part 1, pp. 1332–1347, 1998.

[27] V. M. Ranieri, G. D. Rubenfeld, B. T. Thompson et al., "Acute respiratory distress syndrome: the Berlin definition," *Journal of the American Medical Association*, vol. 307, no. 23, pp. 2526–2533, 2012.

[28] L. Gattinoni, M. Bombino, P. Pelosi et al., "Lung structure and function in different stages of severe adult respiratory distress syndrome," *Journal of the American Medical Association*, vol. 271, no. 22, pp. 1772–1779, 1994.

[29] L. Gattinoni, P. Caironi, P. Pelosi, and L. R. Goodman, "What has computed tomography taught us about the acute respiratory distress syndrome?" *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 9, pp. 1701–1711, 2001.

[30] J. B. Borges, V. N. Okamoto, G. F. J. Matos et al., "Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome," *American Journal of Respiratory and Critical Care Medicine*, vol. 174, no. 3, pp. 268–278, 2006.

[31] C. S. V. Barbas, G. F. J. De Matos, M. P. Pincelli et al., "Mechanical ventilation in acute respiratory failure: recruitment and high positive end-expiratory pressure are necessary," *Current Opinion in Critical Care*, vol. 11, no. 1, pp. 18–28, 2005.

[32] B. Lachmann, "Open up the lung and keep the lung open," *Intensive Care Medicine*, vol. 18, no. 6, pp. 319–321, 1992.

[33] G. F. J. de Matos, F. Stanzani, R. H. Passos et al., "How large is the lung recruitability in early acute respiratory distress syndrome: a prospective case series of patients monitored by computed tomography," *Critical Care*, vol. 16, no. 1, Article ID R4, 2012.

[34] M. Karcz, A. Vitkus, P. J. Papadakos, D. Schwaiberger, and B. Lachmann, "State-of-the-Art Mechanical Ventilation," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 26, no. 3, pp. 486–506, 2012.

[35] C. S. V. Barbas, "Understanding and avoiding ventilator-induced lung injury: lessons from an insightful experimental study," *Critical Care Medicine*, vol. 38, no. 12, pp. 2418–2419, 2010.

[36] C. S. Barbas and G. F. de Matos, "Best strategy to recruit primary ARDS: what to look for," *Minerva Anestesiologica*, vol. 76, no. 9, pp. 681–683, 2010.

[37] K. Ichikado, H. Muranaka, Y. Gushima et al., "Fibroproliferative changes on high-resolution CT in the acute respiratory distress syndrome predict mortality and ventilator dependency: a prospective observational cohort study," *BMJ Open*, vol. 2, no. 2, Article ID e000545, 2012.

[38] G. Bellani, T. Mauri, and A. Pesenti, "Imaging in acute lung injury and acute respiratory distress syndrome," *Current Opinion in Critical Care*, vol. 18, no. 1, pp. 29–34, 2012.

[39] N. De Prost, M. R. Tucci, and M. F. Vidal Melo, "Assessment of lung inflammation with ^{18}F-FDG PET during acute lung injury," *American Journal of Roentgenology*, vol. 195, no. 2, pp. 292–300, 2010.

[40] G. Bellani, C. Messa, L. Guerra et al., "Lungs of patients with acute respiratory distress syndrome show diffuse inflammation in normally aerated regions: a [^{18}F]-fluoro-2-deoxy-D-glucose PET/CT study," *Critical Care Medicine*, vol. 37, no. 7, pp. 2216–2222, 2009.

[41] B. Bouhemad, H. Brisson, M. Le-Guen, C. Arbelot, Q. Lu, and J. J. Rouby, "Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment," *American Journal of Respiratory and Critical Care Medicine*, vol. 183, no. 3, pp. 341–347, 2011.

[42] E. L. V. Costa, P. G. Lima, and M. B. R. Amato, "Electrical impedance tomography," *Current Opinion in Critical Care*, vol. 15, no. 1, pp. 18–24, 2009.

[43] E. L. V. Costa, J. B. Borges, A. Melo et al., "Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography," *Intensive Care Medicine*, vol. 35, no. 6, pp. 1132–1137, 2009.

[44] C. Gomez-Laberge, J. H. Arnold, and G. K. Wolf, "A unified approach for EIT imaging of regional overdistension and atelectasis in acute lung injury," *IEEE Transactions on Medical Imaging*, vol. 31, no. 3, Article ID 6127914, pp. 834–842, 2012.

[45] A. Adler, M. B. Amato, J. H. Arnold et al., "Whither lung EIT: where are we, where do we want to go and what do we need to get there?" *Physiological Measurement*, vol. 33, no. 5, pp. 679–694, 2012.

[46] S. P. Keenan, T. Sinuff, D. J. Cook, and N. S. Hill, "Does noninvasive positive pressure ventilation improve outcome in acute hypoxemic respiratory failure? A systematic review," *Critical Care Medicine*, vol. 32, no. 12, pp. 2516–2523, 2004.

[47] Q. Zhan, B. Sun, L. Liang et al., "Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial," *Critical Care Medicine*, vol. 40, no. 2, pp. 455–460, 2012.

[48] R. G. Brower, M. A. Matthay, A. Morris, D. Schoenfeld, B. T. Thompson, and A. Wheeler, "Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute

lung injury and the acute respiratory distress syndrome," *New England Journal of Medicine*, vol. 342, no. 18, pp. 1301–1308, 2000.

[49] K. E. A. Burns, N. K. J. Adhikari, A. S. Slutsky et al., "Pressure and volume limited ventilation for the ventilatory management of patients with acute lung injury: a systematic review and meta-analysis," *PLoS ONE*, vol. 6, no. 1, Article ID e14623, 2011.

[50] M. B. P. Amato, T. E. Stewart, L. Brochard et al., "Effects of superimposed driving-pressure on mortality in patients with acute lung injury or acute respiratory distress syndrome," *The Journal of the American Medical Association*. In press.

[51] M. B. P. Amato, C. S. V. Barbas, D. M. Medeiros et al., "Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome," *New England Journal of Medicine*, vol. 338, no. 6, pp. 347–354, 1998.

[52] J. Villar, R. M. Kacmarek, L. Pérez-Méndez, and A. Aguirre-Jaime, "A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial," *Critical Care Medicine*, vol. 34, no. 5, pp. 1311–1318, 2006.

[53] V. M. Ranieri, P. M. Suter, C. Tortorella et al., "Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial," *Journal of the American Medical Association*, vol. 282, no. 1, pp. 54–61, 1999.

[54] S. R. R. Vieira, L. Puybasset, Q. Lu et al., "A scanographic assessment of pulmonary morphology in acute lung injury: significance of the lower inflection point detected on the lung pressure- volume curve," *American Journal of Respiratory and Critical Care Medicine*, vol. 159, no. 5 I, pp. 1612–1623, 1999.

[55] J. C. Richard, S. M. Maggiore, B. Jonson, J. Mancebo, F. Lemaire, and L. Brochard, "Influence of tidal volume on alveolar recruitment: respective role of PEEP and a recruitment maneuver," *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 7, pp. 1609–1613, 2001.

[56] A. A. Maung and L. J. Kaplan, "Airway pressure release ventilation in acute respiratory distress syndrome," *Critical Care Clinics*, vol. 27, no. 3, pp. 501–509, 2011.

[57] A. Modrykamien, R. L. Chatburn, and R. W. Ashton, "Airway pressure release ventilation: an alternative mode of mechanical ventilation in acute respiratory distress syndrome," *Cleveland Clinic Journal of Medicine*, vol. 78, no. 2, pp. 101–110, 2011.

[58] X. Z. Wang, C. J. Lü, F. Q. Gao, X. H. Li, D. Hao, and F. Y. Ning, "Comparison of the effects of BiPAP ventilation combined with lung recruitment maneuvers and low tidal volume A/C ventilation in patients with acute respiratory distress syndrome," *Zhonghua Jie He He Hu Xi Za Zhi*, vol. 30, no. 1, pp. 44–47, 2007.

[59] P. M. Spieth, A. R. Carvalho, A. Güldner et al., "Pressure support improves oxygenation and lung protection compared to pressure-controlled ventilation and is further improved by random variation of pressure support," *Critical Care Medicine*, vol. 39, no. 4, pp. 746–755, 2011.

[60] M. Gama De Abreu, P. M. Spieth, P. Pelosi et al., "Noisy pressure support ventilation: a pilot study on a new assisted ventilation mode in experimental lung injury," *Critical Care Medicine*, vol. 36, no. 3, pp. 818–827, 2008.

[61] T. Yoshida, A. Uchiyama, N. Matsuura, T. Mashimo, and Y. Fujino, "Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury," *Critical Care Medicine*, vol. 40, no. 5, pp. 1578–1585, 2012.

[62] D. Y. Huang, J. Liu, X. Y. Wu et al., "Effects of neurally adjusted ventilatory adjusted ventilatory assist on prevention of ventilator-induced diaphragmatic dysfunction in acute respiratory distress syndrome rabitts.," *Zhonghua Jie He He Hu Xi Za Zhi*, vol. 34, no. 4, pp. 288–293, 2011.

[63] X. Y. Wu, Y. Z. Huang, Y. Yang, S. Q. Liu, H. G. Liu, and H. B. Qiu, "Effects of neurally adjusted ventilatory assist on patient-ventilator synchrony in patients with acute respiratory distress syndrome," *Zhonghua Jie He He Hu Xi Za Zhi*, vol. 32, no. 7, pp. 508–512, 2009.

[64] S. Sud, M. Sud, J. O. Friedrich et al., "High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis," *BMJ*, vol. 340, article c2327, 2010.

[65] F. Abroug, L. Ouanes-Besbes, F. Dachraoui, I. Ouanes, and L. Brochard, "An updated study-level meta-analysis of randomised controlled trials on proning in ARDS and acute lung injury," *Critical Care*, vol. 15, no. 1, article no. R6, 2011.

[66] L. Gattinoni, E. Carlesso, P. Taccone, F. Polli, C. Guérin, and J. Mancebo, "Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis," *Minerva Anestesiologica*, vol. 76, no. 6, pp. 448–454, 2010.

[67] P. Squara, J. F. A. Dhainaut, A. Artigas, and J. Carlet, "Hemodynamic profile in severe ARDS: results of the European collaborative ARDS study," *Intensive Care Medicine*, vol. 24, no. 10, pp. 1018–1028, 1998.

[68] H. P. Wiedemann, A. P. Wheeler, G. R. Bernard et al., "Comparison of two fluid-management strategies in acute lung injury," *New England Journal of Medicine*, vol. 354, no. 24, pp. 2564–2575, 2006.

[69] T. M. Bull, B. Clark, K. McFann, and M. Moss, "Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury," *American Journal of Respiratory and Critical Care Medicine*, vol. 182, no. 9, pp. 1123–1128, 2010.

[70] A. Mekontso Dessap, F. Boissier, R. Leon et al., "Prevalence and prognosis of shunting across patent foramen ovale during acute respiratory distress syndrome," *Critical Care Medicine*, vol. 38, no. 9, pp. 1786–1792, 2010.

[71] W. M. Zapol, M. T. Snider, and J. D. Hill, "Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study," *Journal of the American Medical Association*, vol. 242, no. 20, pp. 2193–2196, 1979.

[72] L. Gattinoni, E. Carlesso, and T. Langer, "Clinical review: extracorporeal membrane oxygenation," *Critical Care*, vol. 15, no. 6, Article ID 243, 2011.

[73] D. Brodie and M. Bacchetta, "Extracorporeal membrane oxygenation for ARDS in adults," *New England Journal of Medicine*, vol. 365, no. 20, pp. 1905–1914, 2011.

[74] G. J. Peek, M. Mugford, R. Tiruvoipati et al., "Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial," *The Lancet*, vol. 374, no. 9698, pp. 1351–1363, 2009.

[75] V. M. Ranieri, P. P. Terragni, L. Del Sorbo et al., "Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal," *Anesthesiology*, vol. 111, no. 4, pp. 826–835, 2009.

[76] M. Zimmermann, T. Bein, M. Arlt et al., "Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study," *Critical Care*, vol. 13, no. 1, article no. R10, 2009.

[77] T. M. Bingold, B. Scheller, T. Wolf et al., "Superimposed high-frequency jet ventilation combined with continuous positive airway pressure/assisted spontaneous breathing improves oxygenation in patients with H1N1-associated ARDS," *Annals of Intensive Care*, vol. 2, no. 1, pp. 1–5, 2012.

[78] T. Varpula, I. Jousela, R. Niemi, O. Takkunen, and V. Pettilä, "Combined effects of prone positioning and airway pressure release ventilation on gas exchange in patients with acute lung injury," *Acta Anaesthesiologica Scandinavica*, vol. 47, no. 5, pp. 516–524, 2003.

[79] G. Rival, C. Patry, N. Floret, J. C. Navellou, E. Belle, and G. Capellier, "Prone position and recruitment manoeuvre: the combined effect improves oxygenation," *Critical Care*, vol. 15, no. 3, article no. R125, 2011.

[80] M. Lubnow, A. Luchner, A. Philipp et al., "Combination of high frequency oscillatory ventilation and interventional lung assist in severe acute respiratory distress syndrome," *Journal of Critical Care*, vol. 25, no. 3, pp. 436–444, 2010.

[81] C. C. Sheu, M. N. Gong, R. Zhai et al., "Clinical characteristics and outcomes of sepsis-related vs non-sepsis-related ARDS," *Chest*, vol. 138, no. 3, pp. 559–567, 2010.

[82] C.-T. Luyt, A. Combes, J.-L. Trouillet, A. Nieszkowska, and J. Chastre, "Virus-induced acute respiratory distress syndrome: epidemiology, management and outcome," *Presse Medicale*, vol. 40, no. 12 PART 2, pp. e561–e568, 2011.

[83] A. G. Proudfoot, M. Hind, and M. J. D. Griffiths, "Biomarkers of acute lung injury: worth their salt?" *BMC Medicine*, vol. 9, Article ID 132, pp. 132–139, 2011.

[84] J. G. Clark, J. A. Milberg, K. P. Steinberg, and L. D. Hudson, "Type III procollagen peptide in the adult respiratory distress syndrome. Association of increased peptide levels in bronchoalveolar lavage fluid with increased risk for death," *Annals of Internal Medicine*, vol. 122, no. 1, pp. 17–23, 1995.

[85] S. Karlsson, M. Heikkinen, V. Pettilä et al., "Predictive value of procalcitonin decrease in patients with severe sepsis: a prospective observational study," *Critical Care*, vol. 14, no. 6, article no. R205, 2010.

[86] L. Bouadma, C. E. Luyt, F. Tubach et al., "Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial," *The Lancet*, vol. 375, no. 9713, pp. 463–474, 2010.

[87] E. Rivers, B. Nguyen, S. Havstad et al., "Early goal-directed therapy in the treatment of severe sepsis and septic shock," *New England Journal of Medicine*, vol. 345, no. 19, pp. 1368–1377, 2001.

[88] E. P. Rivers, M. Katranji, K. A. Jaehne et al., "Early interventions in severe sepsis and septic shock: a review of the evidence one decade later," *Minerva Anestesiologica*, vol. 78, no. 6, pp. 712–724, 2012.

[89] T. R. Craig, M. J. Duffy, M. Shyamsundar et al., "Extravascular lung water indexed to predicted body weight is a novel predictor of intensive care unit mortality in patients with acute lung injury," *Critical Care Medicine*, vol. 38, no. 1, pp. 114–120, 2010.

[90] C. C. Sheu, M. N. Gong, R. Zhai et al., "The influence of infection sites on development and mortality of ARDS," *Intensive Care Medicine*, vol. 36, no. 6, pp. 963–970, 2010.

[91] C. R. Cooke, J. M. Kahn, E. Caldwell et al., "Predictors of hospital mortality in a population-based cohort of patients with acute lung injury," *Critical Care Medicine*, vol. 36, no. 5, pp. 1412–1420, 2008.

[92] L. Papazian, J. M. Forel, A. Gacouin et al., "Neuromuscular blockers in early acute respiratory distress syndrome," *New England Journal of Medicine*, vol. 363, no. 12, pp. 1107–1116, 2010.

[93] A. Afshari, J. Brok, A. M. Møller, and J. Wetterslev, "Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults," *Cochrane Database of Systematic Reviews*, vol. 7, Article ID CD002787, 2010.

[94] K. P. Steinberg, L. D. Hudson, R. B. Goodman et al., "Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome," *New England Journal of Medicine*, vol. 354, no. 16, pp. 1671–1684, 2006.

[95] N. Seam, G. U. Meduri, H. Wang et al., "Effects of methylprednisolone infusion on markers of inflammation, coagulation, and angiogenesis in early acute respiratory distress syndrome," *Critical Care Medicine*, vol. 40, no. 2, pp. 495–501, 2012.

[96] M. A. Matthay, R. G. Brower, B. T. Thompson et al., "Randomized, placebo-controlled trial of an aerosolized beta-2 adrenergic agonist (Albuterol) for the treatment of acute lung injury," *American Journal of Respiratory and Critical Care Medicine*, vol. 179, Article ID A2166, 2009.

[97] T. W. Rice, B. T. Tompson, E. Smoot et al., "Omega-3 (n-3) fatty acid, gamma- linoleic acid (GLA) and anti-oxidant supplementation in acute lung injury (OMEGA trial)," *Critical Care Medicine*, vol. 37, article A408, 2009.

[98] T. W. Rice, A. P. Wheeler, B. T. Thompson et al., "Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial," *Journal of the American Medical Association*, vol. 307, no. 8, pp. 795–803, 2012.

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 428798, 6 pages
doi:10.1155/2012/428798

Clinical Study

Derecruitment Test and Surfactant Therapy in Patients with Acute Lung Injury

Alexey A. Smetkin,[1,2,3] Vsevolod V. Kuzkov,[1,2] Konstantin M. Gaidukov,[1,2] Lars J. Bjertnaes,[3] and Mikhail Y. Kirov[1,2,3]

[1] *Department of Anesthesiology and Intensive Care Medicine, Northern State Medical University, Troitsky Avenue 51, Arkhangelsk 163000, Russia*
[2] *Department of Anesthesiology and Intensive Care Medicine, City Hospital No. 1 of Arkhangelsk, Suvorov Street 1, Arkhangelsk 163001, Russia*
[3] *Department of Clinical Medicine (Anesthesiology), Faculty of Medicine, University of Tromsoe, MH-Breivika, 9038 Tromsoe, Norway*

Correspondence should be addressed to Mikhail Y. Kirov, mikhail_kirov@hotmail.com

Received 10 May 2012; Accepted 5 July 2012

Academic Editor: Zsolt Molnar

Introduction. A recruitment maneuver (RM) may improve gas exchange in acute lung injury (ALI). The aim of our study was to assess the predictive value of a derecruitment test in relation to RM and to evaluate the efficacy of RM combined with surfactant instillation in patients with ALI. *Materials and Methods*. Thirteen adult mechanically ventilated patients with ALI were enrolled into a prospective pilot study. The patients received protective ventilation and underwent RM followed by a derecruitment test. After a repeat RM, bovine surfactant (*surfactant group*, $n = 6$) or vehicle only (*conventional therapy group*, $n = 7$) was instilled endobronchially. We registered respiratory and hemodynamic parameters, including extravascular lung water index (EVLWI). *Results*. The derecruitment test decreased the oxygenation in 62% of the patients. We found no significant correlation between the responses to the RM and to the derecruitment tests. The baseline EVLWI correlated with changes in SpO_2 following the derecruitment test. The surfactant did not affect gas exchange and lung mechanics but increased EVLWI at 24 and 32 hrs. *Conclusions*. Our study demonstrated no predictive value of the derecruitment test regarding the effects of RM. Surfactant instillation was not superior to conventional therapy and might even promote pulmonary edema in ALI.

1. Introduction

Acute lung injury (ALI) is associated with significant morbidity and mortality in critically ill patients [1–3]. Several mechanisms are involved in the development of ALI. The enhanced pulmonary capillary leakage causing pulmonary edema is one of the key factors. Another important mechanism is the formation of atelectases secondary to depletion of surfactant and accumulation of lung tissue fluid [4–6]. The latter mechanisms in combination with derangement of hypoxic pulmonary vasoconstriction may cause increased venous admixture and progressive deterioration of oxygenation [4, 7, 8].

The recruitment maneuver (RM) is a widely used technique aiming to reopen atelectatic lung areas in patients with ALI. Transient increase in the airway pressure up to 40–60 cm H_2O for 40–60 sec reexpands the deaerated lung tissue areas and improves oxygenation [9–11]. However, the influence of RM on the outcome is controversial [12, 13]. Moreover, RM has a number of adverse effects; the most significant of those are barotrauma and cardiovascular collapse [14–17]. The risks of RM are justified predominantly in potential responders, necessitating a search for tests that can predict the response to the maneuver.

The airway suctioning procedures require deliberate disconnection of airway tubes thereby reducing PEEP to 0 cm H_2O. This may lead to alveolar derecruitment that produces effects opposite to those of the RM [18]. The most prominent of these effects are reduction of lung compliance and significant decrease in arterial oxygenation. We hypothesized

that changes in oxygenation and lung mechanics at the time of derecruitment may be dependent on the antiatelectatic potential related to the response to RM, and thus, prevent its use in potential nonresponders.

Depletion of surfactant is an important factor predisposing to formation of atelectases and alveolar consolidation in patients with ALI. In patients with surfactant deficiency and alveolar instability, RM may be followed by hypoxemia and rapid reconsolidation of lung tissue [19]. Taking this theoretical background into account, the combination of RM and surfactant therapy could be of potential benefit in patients with ALI.

Therefore our study had two goals: (1) to explore whether the efficacy of RM might be predicted on the basis of changes in oxygenation and lung mechanics provoked by the derecruitment maneuver, and (2) to assess the effects of RM combined with endobronchial instillation of surfactant in patients with ALI.

2. Materials and Methods

The study was conducted in compliance with the Helsinki Declaration. The study protocol and the informed consent form were approved by the Ethics Committee of Northern State Medical University, Arkhangelsk, Russian Federation. Written informed consent was obtained from every patient or next of kin.

Thirteen adult patients with ALI requiring mechanical ventilation (MV) were enrolled into the pilot study. All the patients met the ALI criteria of the American-European Consensus Conference [20]. Exclusion criteria were anticipated duration of MV of less than 24 hours, duration of ALI more than 24 hours before the start of study, and inability to perform alveolar recruitment maneuver due to comorbidities. The severity of illness at the entry of study was estimated using SAPS II score. The severity of organ dysfunction and lung injury were assessed at the start of study and at 24 and 48 hrs employing the SOFA score and the lung injury score (LIS), respectively. Patients were sedated with fentanyl (1 mcg/kg/hr) and midazolam (0.05 mg/kg/hr) and ventilated using pressure-controlled ventilation (Avea, VIASYS Heathcare, USA) with the following baseline ventilator settings: tidal volume 7 mL/kg of predicted body weight, FiO_2 0.5, and PEEP 4 cm H_2O. The respiratory rate was adjusted to maintain $PaCO_2$ of 35–45 mm Hg. If these settings did not result in a $SaO_2 \geq 92\%$, FiO_2 was increased by steps of 0.1 every two minutes up to 0.8.

We recorded parameters of mechanical ventilation including tidal volume (V_T), inspiratory oxygen fraction (FiO_2), peak airway pressure (P_{peak}), mean airway pressure (P_{mean}), positive end-expiratory pressure (PEEP), and respiratory compliance (C). In parallel, we analyzed arterial blood gases including pH, $PaCO_2$, PaO_2, SaO_2, base excess (BE), and lactate concentration. The end-tidal CO_2 ($EtCO_2$) was registered using Capnostream TM monitor (Oridion, Israel).

All the patients were cannulated with a 5 F femoral artery catheter (Pulsiocath PV2015L20, Pulsion) and an 8.5 F jugular central venous catheter (triple-lumen 20 cm catheter). The hemodynamic monitoring was performed using the single transpulmonary thermodilution technique with $PiCCO_2$ monitor (Pulsion Medical Systems, Germany). The thermodilution measurements were performed in triplicate with injections of ice-cold (<8°C) 5% dextrose solution via a central venous catheter. The registered hemodynamic parameters included central venous pressure (CVP), cardiac index (CI), mean arterial pressure (MAP), stroke volume index (SVI), systemic vascular resistance index (SVRI), heart rate (HR), global ejection fraction (GEF), left ventricle contractility index (dPmx), global end-diastolic volume index (GEDVI), and extravascular lung water index (EVLWI) adjusted to predicted body weight (PBW), which was calculated as follows: PBW (kg) = 50+2.3 (height (cm)/2.54–60) for male, and PBW (kg) = 45+2.3 (height (cm)/2.54–60) for female.

2.1. Recruitment Maneuver. After baseline measurements and muscular blockade with pipecuronium (0.06 mg/kg), RM was performed by applying a continuous positive airway pressure of 40 cm H_2O for a period of 40 seconds [9, 21]. The recruitment maneuver was discontinued in case of hypotension (MAP < 50 mm Hg, or a decrease in MAP by more than by 30 mm Hg from the initial value), or hypoxemia (SpO_2 < 85% or a decrease by more than 10%). Then, pressure-controlled ventilation was resumed with the same settings as before RM. The level of PEEP was set at 2 cm H_2O above the lower inflection point (LIP) of the pressure-volume (P-V) curve determined by an inflection point maneuver of the ventilator, but not less than 4 cm H_2O.

The arterial blood gases, SpO_2, V_T, and $EtCO_2$ were registered at 5 min after the RM. The efficacy of the RM was assessed by detecting the changes in SpO_2 and V_T. Patients were defined as responders if the absolute SpO_2 value increased by at least 2% or V_T rose by at least 10% [10]. The stability of the RM was assessed by registering the changes in SpO_2, V_T, and $EtCO_2$ at 5 min intervals during the subsequent 30 min period. The RM was considered as stable if the absolute value of SpO_2 decreased by ≤2% or V_T decreased by ≤5%.

2.2. Derecruitment Test. After the assessment of RM stability, the derecruitment test was performed. Positive end-expiratory pressure was set at 0 cm H_2O for a period of 15 minutes. Other parameters of mechanical ventilation were unchanged. The changes in SpO_2, V_T, and $EtCO_2$ were registered every five minutes. At the end of the derecruitment test, we analyzed the arterial blood gases. The derecruitment test was interrupted in case of severe hypoxia (SpO_2 < 85%). The test was defined as positive if it resulted in a decrease in SpO_2 by at least 2% and in V_T by at least 10%, respectively.

2.3. Surfactant Therapy. After the derecruitment test, PEEP was adjusted to the previous value. The patients were randomized, by means of the sealed envelope method, to a surfactant therapy group (ST group, $n = 6$), and a conventional therapy group (CT group, $n = 7$). Physicians and research staff were not blinded to the study groups. The ST group received the surfactant emulsion (Surfactant-BL, Biosurf, Russia) prepared *ex tempore* and administered

into the segmental bronchi in a total dose of 6.0 mg/kg of PBW (0.4 mL/kg of PBW) by means of fiberoptic bronchoscopy (FOB) according to the recommendations of the manufacturer. The CT group received an equivalent volume of 0.9% NaCl endobronchially. After FOB and instillation of surfactant emulsion or 0.9% NaCl, the RM was repeated followed by adjustment of PEEP. The FOB with instillation of the study medicine was repeated at 18 hrs and 32 hrs.

Arterial blood gases and parameters of hemodynamics and mechanical ventilation were registered at 1, 2, 4, 8, 16, 24, 32, and 48 hrs after the initial instillation of surfactant emulsion or 0.9% NaCl.

2.4. Statistical Analysis. For data collection and analysis we used SPSS software (version 18.0; SPSS Inc, Chicago, IL). The data distribution was assessed with Shapiro-Wilk test. Quantitative data were presented as mean ± standard deviation or median (25th–75th percentile) depending on the data distribution. The discrete data were expressed as absolute values or percentages. In case of normal distribution, we used Student's t-test for comparisons between groups. Nonparametrically distributed data were assessed by the Mann-Whitney U-test. The correlation analysis was performed using Pearson's or Spearman's tests for parametrically and nonparametrically distributed data, respectively. The discrete data were evaluated using chi-square test. For all tests, a P value < 0.05 was considered as significant.

3. Results

The individual demographic and clinical characteristics of the patients are presented in Table 1. At the study entry, patients had a mean SAPS II score of 40 ± 13 points and a mean SOFA score of 8.7 ± 3.0 points. During the study, the severity of organ dysfunction decreased slightly to SOFA score of 7.4 ± 3.3 at 48 hrs. Initially, the patients had severe lung injury accompanied by a LIS of 2.5 ± 0.7 points. During the study, LIS did not change significantly. The severity of organ dysfunction and lung injury did not differ between the study groups.

In response to the RM, the changes in SpO_2 correlated with the changes in PaO_2 ($r = 0.79$, $P < 0.01$). As evaluated by the changes in SpO_2, the RM was successful in 62% of the patients. In parallel, the RM increased the tidal volume significantly (>10%) in 31% of the patients.

The assessment of the stability of the RM revealed a significant decrease in SpO_2 among 50% of the responders and a decline in V_T in 70% of the responders to RM.

The derecruitment test resulted in a decrease in SpO_2 in 62% of the patients and a reduction of V_T in 54% of the patients. During the derecruitment test, SpO_2 decreased in 71% of the responders and 50% of the nonresponders. Most of the patients presented with $SpO_2 \geq 90\%$. In three patients, the derecruitment test was interrupted within 5 min due to a rapidly developing hypoxemia. Following derecruitment, a reduction of V_T was revealed in 100% of the responders to RM and 38% of the nonresponders. We found no correlations between the changes in SpO_2 and V_T in response to the RM or to the derecruitment test. The changes in PaO_2 after RM correlated inversely with changes in V_T during the derecruitment test ($r = -0.72$, $P < 0.05$).

We found no significant differences regarding the effects of RM and the derecruitment test in patients with direct and nondirect ALI.

The baseline EVLWI correlated with changes in SpO_2 during the derecruitment test ($r = 0.7$, $P < 0.05$), but did not correlate with changes in V_T.

The changes in volumetric parameters, blood gases and lung mechanics are presented in Table 2. After performing the tests and at 16 hrs, $PaCO_2$ was significantly higher in the ST group. The surfactant therapy did neither affect PaO_2/FiO_2, $PaCO_2$, and $EtCO_2$, nor minute volume of ventilation, respiratory compliance, selected PEEP values, or FiO_2. However, the ST group demonstrated a significant increase in EVLWI at 24 and 32 hrs.

4. Discussion

Our study demonstrated no predictive value of the derecruitment test regarding its possibility to uncover effects of RM in patients with ALI. This necessitates a search for alternative predictors of the response to alveolar recruitment. Moreover, the endobronchial instillation of surfactant was not superior to conventional therapy in patients with ALI, and our study revealed that it might even worsen the development of pulmonary edema.

4.1. Recruitment and Derecruitment. The changes in SpO_2 we noticed during RM correlated with the changes in PaO_2. This allowed us to assess oxygenation continuously by means of SpO_2, which is more readily available at the bedside, as compared to frequent blood gases analyses. Identifying responders to RM, we used the cut-off value of $SpO_2 \geq 2\%$, which is the average increase in SpO_2, as demonstrated by *The ARDS Clinical Trials Network* [10]. In contrast to SpO_2, V_T increased only in one-third of the patients. Moreover, the recruitment effects were unstable in the majority of patients. These findings may be explained by a prevalence of direct lung injury due to pneumonia (77% of the studied patients) that demonstrate less effective recruitment maneuver and a predisposition to formation of atelectases [21–23].

The high rate of desaturation and pulmonary recollapse following the derecruitment test reflect changes that can be observed in response to airway disconnection. The lack of a predictive value of the supposed derecruitment test might be explained by the different pattern of changes in ventilation-perfusion interaction during alveolar recruitment and derecruitment [24, 25]. However, the inverse correlation between the changes in PaO_2 after the RM and the changes in V_T during the derecruitment test demonstrates that patients with lack of improvement of oxygenation during the RM are more predisposed to recollapse of alveoli during the derecruitment. It might be explained by a predominance of the mechanisms of lung consolidation rather than by pulmonary edema in this group of patients. This speculation corresponds to the absence of correlation between changes in V_T during desaturation and the baseline value of EVLWI. In contrast, the correlation between the baseline EVLWI and

Table 1: Demographic and clinical characteristics of patients with acute lung injury.

Patient	Group	Diagnosis	Age, years	Gender	Height, cm	Weight, kg	SAPS II, points	SOFA, points	LIS, points	PaO_2/FiO_2, mm Hg	$PaCO_2$, mm Hg
1	ST	Pancreatitis	56	m	170	75	30	5	1.70	268	48.9
2	ST	Pneumonia	68	m	171	77	48	9	1.50	185	43.4
3	ST	Pneumonia	57	m	175	80	46	8	2.25	155	50.5
4	CT	Pneumonia	66	m	162	60	44	9	1.75	200	32.9
5	CT	Pneumonia	33	m	180	70	37	12	2.75	73	44.4
6	CT	Peritonitis	78	f	162	85	66	9	1.75	240	41.7
7	ST	Pneumonia	25	m	183	70	25	6	3.67	121	48.6
8	CT	Pneumonia	57	m	175	75	46	11	2.00	125	49.9
9	CT	Pneumonia	31	f	170	86	22	4	3.25	73	45.4
10	ST	Fat embolism	27	m	178	75	28	5	2.75	189	41.7
11	ST	Pneumonia	52	m	176	90	31	10	3.25	45	55.7
12	CT	Pneumonia	51	m	175	78	45	14	2.50	71	57.0
13	CT	Pneumonia	72	m	175	120	54	11	3.00	83	42.7

Data are presented as absolute values.
ST: surfactant therapy; CT: conventional therapy; LIS: lung injury score; m: male; f: female.

the severity of desaturation during the derecruitment test demonstrates a predisposition of patients with lung edema to more severe hypoxemia following derecruitment. These results confirm the potential risk of airway disconnection and should be considered during tracheal suctioning of patients with ALI.

4.2. Surfactant Therapy. Our study demonstrated a lack of effect of surfactant therapy in combination with RM in patients with ALI. As evidenced by a recent metaanalysis, these findings are consistent with the results of most of the previous studies in this field [26]. An explanation of the negative result could be that administration of surfactant took place in patients in whom pulmonary edema already had developed, as confirmed by increased EVLWI. We cannot exclude the possibility that alveolar fluid might have inactivated both endogenously produced and exogenously administered surfactant. On the other hand, it could be potentially harmful to restore an assumed lack of surfactant without preassessment of the actual deficit. Therefore, further investigations are required with special focus on the efficacy of surfactant replacement therapy in patients with confirmed surfactant insufficiency.

Although the surfactant treatment used in this study did not influence lung mechanics or alveolar gas exchange, it unexpectedly resulted in enhancement of lung edema. In a recent study by Lu et al. using computed tomography, it has been shown that instillation of exogenous surfactant in patients with ALI/acute respiratory distress syndrome (ARDS) caused substantial expansion of nonaerated lung areas [27]. Several mechanisms might be involved in the progression of lung edema. One of the possible mechanisms is the retention of lung water by hydrophilic components of the surfactant proteins. Another mechanism could be an inflammatory reaction, which is evoked by an interaction between the exogenously administered surfactant and the active endogenous surfactant resulting in capillary leakage and increase in lung edema [28]. Last but not least, improvement of lung tissue aeration and attenuation of pulmonary hypoxic vasoconstriction may extend the contact area between the thermal indicator and the pulmonary vascular bed leading to increase in the measured EVLWI value [29].

Our study has several limitations including a small sample size, heterogeneous patient characteristics, a relatively high prevalence of patients with direct lung injury, and nonblinded treatment with bovine surfactant. The power analysis performed before our study and based on our hypothesis, that surfactant could lead to a 30% increase in PaO_2/FiO_2 with no changes in PaO_2/FiO_2 in the CT group, revealed that assuming a two-sided P value of 0.05 and 80% power, a sample size of 18 patients in each group is required. However, after analysis of our pilot results, we stopped the study prematurely because we found no beneficial effects of the surfactant therapy. Despite we displayed a significant correlation between the changes in SpO_2 and the changes in PaO_2, the use of changes in SpO_2 instead of PaO_2/FiO_2 for assessment of the efficacy of RM may also be a limitation of our study. Thus, the results of this study as well as the use of derecruitment test and the surfactant therapy in ARDS require further investigation in larger clinical trials.

5. Conclusions

In ALI, the derecruitment test appears to have no predictive value in terms of assessing a potential effect of the alveolar recruitment maneuver. Surfactant therapy combined with RM does not seem to provide any further benefit in comparison with RM and conventional therapy and may even promote lung edema in patients with ALI or ARDS.

Table 2: Changes in hemodynamics, arterial blood gases, and lung mechanics in patients with acute lung injury.

Parameter	Group	After the tests	After the FOB	1 hr	2 hrs	4 hrs	8 hrs	16 hrs	24 hrs	32 hrs	48 hrs
CI, L/min/m^2	ST	5.03 ± 1.04	4.77 ± 1.16	5.05 ± 1.10	4.79 ± 1.20	4.98 ± 1.15	4.99 ± 1.35	4.89 ± 1.16	4.62 ± 1.03	4.76 ± 0.93	4.35 ± 0.74
	CT	3.85 ± 1.84	3.90 ± 1.86	3.66 ± 2.09	3.80 ± 1.88	4.20 ± 2.37	3.96 ± 1.82	3.63 ± 1.81	2.75 ± 0.83	3.23 ± 1.10	3.42 ± 1.23
GEDVI, mL/m^2	ST	863 ± 180	690 ± 88	743 ± 206	799 ± 243	797 ± 218	787 ± 142	752 ± 173	743 ± 207	800 ± 275	714 ± 89
	CT	694 ± 131	675 ± 149	714 ± 172	755 ± 156	749 ± 145	727 ± 111	676 ± 140	694 ± 84	660 ± 108	710 ± 97
EVLWI, mL/kg PBW	ST	19 ± 6	23 ± 5	17 ± 6	18 ± 8	17 ± 5	18 ± 4	19 ± 4	18 ± 5[a]	18 ± 3[a]	18 ± 5
	CT	14 ± 4	15 ± 5	14 ± 6	16 ± 7	14 ± 6	13 ± 6	15 ± 8	11 ± 2	10 ± 3	11 ± 5
PaO_2/FiO_2, mm Hg	ST	157 ± 62	142 ± 41	131 ± 49	159 ± 58	168 ± 71	147 ± 45	162 ± 126	146 ± 32	219 ± 98	189 ± 41
	CT	119 ± 40	154 ± 79	139 ± 50	142 ± 46	162 ± 76	168 ± 75	188 ± 89	196 ± 99	205 ± 84	195 ± 107
$PaCO_2$, mm Hg	ST	56 ± 9[a]	58 ± 9	53 ± 8	51 ± 7	49 ± 11	50 ± 11	54 ± 8[a]	50 ± 15	44 ± 11	47 ± 17
	CT	45 ± 6	44 ± 11	42 ± 10	44 ± 11	41 ± 11	41 ± 11	40 ± 6	40 ± 3	41 ± 3	43 ± 4
$EtCO_2$, mm Hg	ST	44 ± 7	45 ± 7	43 ± 7	42 ± 6	40 ± 5	40 ± 6	39 ± 5	40 ± 11	38 ± 9	41 ± 12
	CT	33 ± 10	37 ± 11	34 ± 11	33 ± 9	32 ± 8	34 ± 8	33 ± 7	31 ± 6	33 ± 6	37 ± 6
FiO_2	ST	0.58 ± 0.20	0.63 ± 0.25	0.70 ± 0.22	0.63 ± 0.15	0.62 ± 0.13	0.58 ± 0.13	0.64 ± 0.16	0.59 ± 0.08	0.56 ± 0.08	0.50 ± 0.06
	CT	0.67 ± 0.14	0.70 ± 0.18	0.63 ± 0.11	0.63 ± 0.11	0.62 ± 0.11	0.59 ± 0.11	0.58 ± 0.10	0.54 ± 0.05	0.56 ± 0.08	0.55 ± 0.04
PEEP, cm H_2O	ST	9 ± 6	11 ± 6	12 ± 7	10 ± 6	10 ± 6	10 ± 7	10 ± 5	11 ± 6	11 ± 6	9 ± 4
	CT	9 ± 4	8 ± 4	9 ± 5	10 ± 5	10 ± 5	9 ± 4	9 ± 4	9 ± 3	9 ± 4	9 ± 4
Compliance, mL/cm H_2O	ST	33 ± 6	33 ± 6	34 ± 5	36 ± 8	37 ± 8	34 ± 8	34 ± 2	31 ± 3	35 ± 3	38 ± 7
	CT	28 ± 7	32 ± 8	31 ± 6	28 ± 5	28 ± 5	30 ± 7	31 ± 9	30 ± 7	32 ± 9	30 ± 7

Data are presented as mean ± standard deviation. [a]intergroup difference ($P < 0.05$).

After the tests: after both recruitment maneuver and de-recruitment test; ST: surfactant therapy; CT: conventional therapy; FOB: fiberoptic bronchoscopy; CI: cardiac index; GEDVI: global end-diastolic volume index; EVLWI: extravascular lung water index; PBW: predicted body weight; PEEP: positive end-expiratory pressure.

References

[1] M. Zambon and J. L. Vincent, "Mortality rates for patients with acute lung injury/ARDS have decreased over time," *Chest*, vol. 133, no. 5, pp. 1120–1127, 2008.

[2] S. E. Erickson, G. S. Martin, J. L. Davis, M. A. Matthay, and M. D. Eisner, "Recent trends in acute lung injury mortality: 1996–2005," *Critical Care Medicine*, vol. 37, no. 5, pp. 1574–1579, 2009.

[3] A. Damluji, E. Colantuoni, P. A. Mendez-Tellez et al., "Short-term mortality prediction for acute lung injury patients: external validation of the Acute Respiratory Distress Syndrome Network prediction model," *Critical Care Medicine*, vol. 39, no. 5, pp. 1023–1028, 2011.

[4] M. H. Kollef and D. P. Schuster, "The acute respiratory distress syndrome," *The New England Journal of Medicine*, vol. 332, no. 1, pp. 27–37, 1995.

[5] L. Gattinoni, P. Caironi, P. Pelosi, and L. R. Goodman, "What has computed tomography taught us about the acute respiratory distress syndrome?" *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 9, pp. 1701–1711, 2001.

[6] R. Maharaj, "Extravascular lung water and acute lung injury," *Cardiology Research and Practice*, vol. 2012, Article ID 407035, 2012.

[7] M. A. Matthay and R. L. Zemans, "The acute respiratory distress syndrome: pathogenesis and treatment," *Annual Review of Pathology*, vol. 6, pp. 147–163, 2011.

[8] D. M. Payen and J. Muret, "Nitric oxide and almitrine: the definitive answer for hypoxemia," *Current Opinion in Anaesthesiology*, vol. 12, no. 1, pp. 37–42, 1999.

[9] J. C. Richard, S. M. Maggiore, and A. Mercat, "Clinical review: bedside assessment of alveolar recruitment," *Critical Care*, vol. 8, no. 3, pp. 163–169, 2004.

[10] R. G. Brower, A. Morris, N. MacIntyre et al., "Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure," *Critical Care Medicine*, vol. 31, no. 11, pp. 2592–2597, 2003.

[11] J. A. Johannigman, S. L. Miller, B. R. Davis, K. Davis, R. S. Campbell, and R. D. Branson, "Influence of low tidal volumes on gas exchange in acute respiratory distress syndrome and the role of recruitment maneuvers," *Journal of Trauma*, vol. 54, no. 2, pp. 320–325, 2003.

[12] J. C. Richard, S. Maggiore, and A. Mercat, "Where are we with recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome?" *Current Opinion in Critical Care*, vol. 9, no. 1, pp. 22–27, 2003.

[13] E. Fan, M. E. Wilcox, R. G. Brower et al., "Recruitment maneuvers for acute lung injury: a systematic review," *American Journal of Respiratory and Critical Care Medicine*, vol. 178, no. 11, pp. 1156–1163, 2008.

[14] I. Morán, E. Zavala, R. Fernández, L. Blanch, and J. Mancebo, "Recruitment manoeuvres in acute lung injury/acute respiratory distress syndrome," *European Respiratory Journal, Supplement*, vol. 22, no. 42, pp. 37s–42s, 2003.

[15] J. Nielsen, M. Østergaard, J. Kjaergaard et al., "Lung recruitment maneuver depresses central hemodynamics in patients following cardiac surgery," *Intensive Care Medicine*, vol. 31, no. 9, pp. 1189–1194, 2005.

[16] S. E. Lapinsky and S. Mehta, "Bench-to-bedside review: recruitment and recruiting maneuvers," *Critical Care*, vol. 9, no. 1, pp. 60–65, 2005.

[17] I. Morán, L. Blanch, R. Fernández, E. Fernández-Mondéjar, E. Zavala, and J. Mancebo, "Acute physiologic effects of a stepwise recruitment maneuver in acute respiratory distress syndrome," *Minerva Anestesiologica*, vol. 77, no. 12, pp. 1167–1175, 2011.

[18] S. Lindgren, H. Odenstedt, C. Olegård, S. Söndergaard, S. Lundin, and O. Stenqvist, "Regional lung derecruitment after endotracheal suction during volume- or pressure-controlled ventilation: a study using electric impedance tomography," *Intensive Care Medicine*, vol. 33, no. 1, pp. 172–180, 2007.

[19] J. F. Lewis and A. Brackenbury, "Role of exogenous surfactant in acute lung injury," *Critical Care Medicine*, vol. 31, supplement 4, pp. S324–S328, 2003.

[20] G. R. Bernard, A. Artigas, K. L. Brigham et al., "The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination," *American Journal of Respiratory and Critical Care Medicine*, vol. 149, no. 3, pp. 818–824, 1994.

[21] D. R. Riva, M. B. G. Oliveira, A. F. Rzezinski et al., "Recruitment maneuver in pulmonary and extrapulmonary experimental acute lung injury," *Critical Care Medicine*, vol. 36, no. 6, pp. 1900–1908, 2008.

[22] M. E. J. Callister and T. W. Evans, "Pulmonary versus extrapulmonary acute respiratory distress syndrome: different diseases or just a useful concept?" *Current Opinion in Critical Care*, vol. 8, no. 1, pp. 21–25, 2002.

[23] P. Pelosi, P. Caironi, and L. Gattinoni, "Pulmonary and extrapulmonary forms of acute respiratory distress syndrome," *Seminars in Respiratory and Critical Care Medicine*, vol. 22, no. 3, pp. 259–268, 2001.

[24] V. M. Ranieri, N. T. Eissa, C. Corbeil et al., "Effects of positive end-expiratory pressure on alveolar recruitment and gas exchange in patients with the adult respiratory distress syndrome," *American Review of Respiratory Disease*, vol. 144, no. 3, pp. 544–551, 1991.

[25] S. M. Maggiore, B. Jonson, J. C. Richard, S. Jaber, F. Lemaire, and L. Brochard, "Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: comparison with the lower inflection point, oxygenation, and compliance," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 5, pp. 795–801, 2001.

[26] W. J. Davidson, D. Dorscheid, R. Spragg, M. Schulzer, E. Mak, and N. T. Ayas, "Exogenous pulmonary surfactant for the treatment of adult patients with acute respiratory distress syndrome: results of a meta-analysis," *Critical Care*, vol. 10, no. 2, article R41, 2006.

[27] Q. Lu, M. Zhang, C. Girardi, B. Bouhemad, J. Kesecioglu, and J. J. Rouby, "Computed tomography assessment of exogenous surfactant-induced lung reaeration in patients with acute lung injury," *Critical Care*, vol. 14, no. 4, article R135, 2010.

[28] J. B. Grotberg, D. Halpern, and O. E. Jensen, "Interaction of exogenous and endogenous surfactant: spreading-rate effects," *Journal of Applied Physiology*, vol. 78, no. 2, pp. 750–756, 1995.

[29] R. B. Easley, D. G. Mulreany, C. T. Lancaster et al., "Redistribution of pulmonary blood flow impacts thermodilution-based extravascular lung water measurements in a model of acute lung injury," *Anesthesiology*, vol. 111, no. 5, pp. 1065–1074, 2009.

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 761051, 14 pages
doi:10.1155/2012/761051

Review Article

Optimization of Preload in Severe Sepsis and Septic Shock

Adil Shujaat and Abubakr A. Bajwa

Division of Pulmonary and Critical Care Medicine, University of Florida College of Medicine-Jacksonville, 655 West 8th Street, Suite 7-088, Jacksonville, FL 32209, USA

Correspondence should be addressed to Adil Shujaat, adil.shujaat@jax.ufl.edu

Received 24 April 2012; Accepted 24 May 2012

Academic Editor: Mikhail Y. Kirov

In sepsis both under- and overresuscitation are associated with increased morbidity and mortality. Moreover, sepsis can be complicated by myocardial dysfunction, and only half of the critically ill patients exhibit preload responsiveness. It is of paramount importance to accurately, safely, and rapidly determine and optimize preload during resuscitation. Traditional methods of determining preload based on measurement of pressure in a heart chamber or volume of a heart chamber ("static" parameters) are inaccurate and should be abandoned in favor of determining preload responsiveness by using one of the "dynamic parameters" based on respiratory variation in the venous or arterial circulation or based on change in stroke volume in response to an endogenous or exogenous volume challenge. The recent development and validation of a number of noninvasive technologies now allow us to optimize preload in an accurate, safe, rapid and, cost-effective manner.

1. Introduction

It is well known that underresuscitation is associated with increased morbidity and mortality in septic shock, and volume resuscitation to optimize preload to improve cardiac output (CO) and blood pressure (BP) is of paramount importance when there is hypovolemia caused by vasodilatation, transudation of fluid into the extravascular compartment, increased insensible fluid loss, and decreased oral intake, in sepsis. On the other hand overzealous resuscitation can also lead to increased morbidity and mortality [1–5]. Moreover, myocardial depression plays a significant role in the pathophysiology of shock in up to 60% of septic patients and can develop at an early stage [6]. Lastly, only about half of the critically ill patients exhibit preload responsiveness [7]—defined as the ability of the heart to increase its stroke volume (SV) in response to an increase in preload. Hence, it is vital that resuscitation in sepsis be guided by accurate assessment and monitoring of hemodynamic status of individual patients.

Traditional methods of determining the adequacy of volume resuscitation have relied on one or another measure of preload, that is, central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), right ventricular end-diastolic volume index (RVEDVI), left ventricular end-diastolic area index (LVEDVAI), and global end-diastolic volume (GEDV)—also known as static parameters of volume status. However, none of these is accurate in predicting preload responsiveness [7–9]. Both pressure and volume measures of preload are affected by multiple factors other than the volume of blood, for example, vascular tone, intrathoracic pressure, and ventricular compliance. Moreover, the Frank-Starling relationship depends upon preload as well as ventricular function. Therefore, it is physiologically impossible to accurately predict preload responsiveness by assessing preload alone. Over the last two decades there has been a paradigm shift in the approach to predicting hypovolemia from measuring preload to actually determining preload responsiveness. Preload responsiveness can be determined by performing a volume challenge maneuver or by making use of the respiratory variation in the venous or arterial circulation—also known as dynamic parameters of volume status.

The volume challenge maneuver comprises a volume challenge and measurement of an end-point, that is, CVP, BP, SV, CO, heart rate (HR), or urine output. The volume challenge can be in the form of an actual administration of

Table 1: Accuracy of various parameters used to predict preload responsiveness [7, 10].

Parameter	Technology	AUC with 95% CI
PLR*	Various methods of CO measurement	0.95 (0.92–0.97)
PPV	Arterial BP waveform	0.94 (0.93–0.95)
SVV	Arterial BP waveform analysis by proprietary algorithm	0.84 (0.78–0.88)
LVEDAI	Echocardiography	0.64 (0.53–0.74)
GEDV	Thermodilution	0.56 (0.37–0.67)
CVP	Central venous catheter	0.55 (0.48–0.62)

PLR: passive leg raising, PPV: pulse pressure variation, SVV: stroke volume variation, LVEDAI: left ventricular end-diastolic area index, GEDV: global end-diastolic volume, CVP: central venous pressure, AUC: area under receiver operating characteristics curve.

intravenous fluid (exogenous and irreversible volume challenge) or a virtual volume challenge where an endogenous volume of blood is displaced from the legs during passive leg raising (PLR) maneuver (endogenous and reversible volume challenge). It is important to realize that SV (or CO), or its surrogate, for example, pulse pressure (PP) or arterial blood flow velocity, is the preferred end-point because a preload responsive heart may not be recognized otherwise. The SV (or CO) can be measured by invasive or noninvasive methods.

Use of respiratory variation in the central venous circulation to predict preload responsiveness comprises measurement of CVP or ultrasonographic measurement of the diameter of either vena cava whereas use of respiratory variation in the arterial circulation to predict preload responsiveness comprises measurement of PP, SV, pulse oximeter plethysmographic (POP) waveform amplitude, or arterial blood flow velocity.

Dynamic parameters of volume status outperform the static ones in predicting preload responsiveness and should be used to optimize preload in severe sepsis and septic shock (Table 1) [7, 10].

2. Dynamic Parameters Used to Predict Preload Responsiveness

(1) Respiratory variation in,

- (a) central venous pressure (CVP),
- (b) vena cava diameter,
  - (i) inferior vena cava (IVC),
  - (ii) superior vena cava (SVC),
- (c) arterial blood pressure waveform-derived variables,
  - (i) pulse pressure variation (PPV),
  - (ii) stroke volume variation (SVV),
- (d) pulse oximeter plethysmographic (POP) waveform amplitude,
- (e) arterial blood flow velocity,
  - (i) aortic,
  - (ii) brachial artery,

(2) passive leg raising (PLR) maneuver,

(3) actual fluid challenge,

3. Respiratory Variation in CVP

Although no single value of CVP can accurately predict preload responsiveness, respiratory changes in CVP can do so. During spontaneous breathing the respiratory changes in pleural pressure can cause cyclic changes in CVP when the right ventricle (RV) is preload responsive than when it is not. An inspiratory fall in CVP indicates that the heart is functioning on the ascending part of the Frank-Starling curve and may or may not respond to volume depending upon how close CVP is to the plateau, whereas lack of an inspiratory fall indicates that the heart is functioning on the flat part of the Frank-Starling curve and will not respond to volume infusion. Therefore, this test is most useful in the negative (see Figure 1).

Magder et al. [11] showed that the lack of an inspiratory fall in CVP of ≥ 1 mmHg predicted lack of preload responsiveness in spontaneously breathing patients including patients triggering breaths on mechanical ventilation. The converse was less predictive; that is, patients who had an inspiratory fall in CVP of >1 mmHg did not always have an increase in CO. In that study volume loading increased the cardiac output in only 1 of 14 patients who did not have an inspiratory fall in CVP whereas it increased the cardiac output in 16 out of 19 patients who had an inspiratory fall in CVP.

Use of respiratory variation in CVP to predict preload responsiveness requires that the inspiratory effort be significant enough to cause a 2 mmHg drop in PAWP, and therefore in the absence of a pulmonary artery catheter (PAC) to confirm such a significant respiratory effort the technique becomes subjective and dependent on observing the patient. Moreover, in a patient who is using expiratory abdominal muscles the release of abdominal muscle contraction may be confused for an inspiratory fall in CVP [12].

4. Respiratory Variation in Diameter of Either Vena Cava

During mechanical ventilation the cyclic effect of positive airway pressure can cause respiratory variation in the diameter of both the SVC and the IVC. This cyclic effect depends upon the transmural pressure of the vessel which is determined by the intravascular pressure—that, in turn, depends on the circulating blood volume and RV function—and by the surrounding pressure, that is, pleural pressure for SVC and

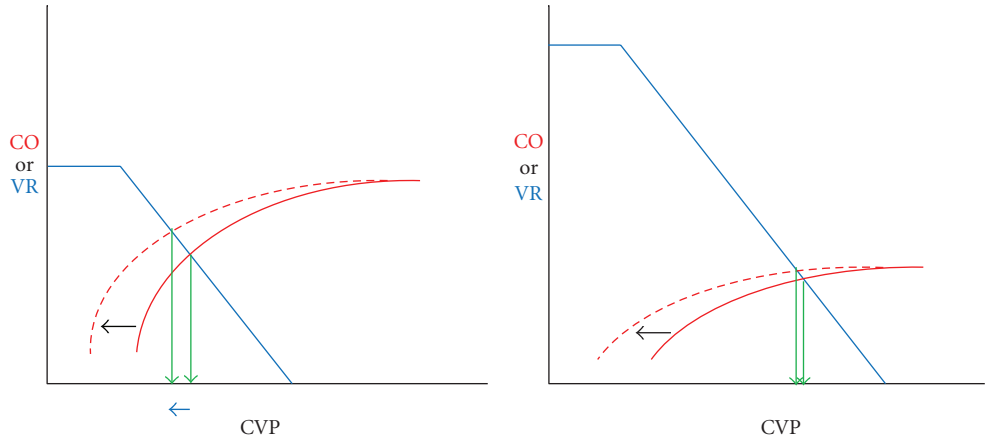


Figure 1: During spontaneous breathing the cardiac function curve (solid red curve) is shifted to the left (dashed red curve). When the heart is functioning on the ascending part of the cardiac function curve. CVP falls (blue arrow) and CO rises ((a), on left). However, when the heart function is depressed or the circulation is volume loaded ((b), on right), CVP and CO remain unchanged. *CVP*: central venous pressure, CO: cardiac output.

abdominal pressure for IVC since the intrathoracic part of the latter vessel is virtual. The SVC diameter is minimal during inspiration and maximal during expiration. On the other hand, since only a minor proportion of positive airway pressure is transmitted to the abdomen, the IVC diameter is maximal during inspiration and minimal during expiration [13].

In two separate studies [14, 15] of septic patients who were on mechanical ventilation, deeply sedated, receiving a tidal volume of ≥8 mL/kg predicted body weight (PBW) and in normal sinus rhythm, respiratory changes in the IVC measured by M-mode ultrasonography (US) were found to be highly accurate in predicting preload responsiveness—defined as an increase in cardiac index (CI) of ≥15% measured by transthoracic echocardiography (TTE). Barbier et al. [14] showed that in the 23 patients in their study an IVC distensibility index of >18% predicted preload responsiveness with a sensitivity of 90% and specificity of 90%. Feissel et al. [15] showed that in the 39 patients in their study an IVC distensibility index of ≥12% predicted preload responsiveness with an NPV of 93% and PPV of 92%. The threshold value of IVC distensibility index is different because the index was calculated differently—Barbier et al. [14] calculated the index as the difference in the maximum diameter of the IVC at end-inspiration and the minimum diameter at end-expiration divided by its minimum diameter at end-expiration and expressed as a percentage whereas Feissel et al. [15] calculated the index as the difference in the diameter of the IVC at end-inspiration and at end-expiration divided by the mean of the two diameters and expressed as a percentage.

In a study of septic patients who were on mechanical ventilation, deeply sedated, receiving a tidal volume of ≥8 mL/kg PBW and in normal sinus rhythm, respiratory changes in the SVC measured by transesophageal echocardiography (TEE) were highly accurate in predicting preload responsiveness—defined as an increase in CI of ≥11%. Vieillard-Baron et al. [16] showed that in the 66 patients in their study an SVC collapsibility index of >36% predicted preload responsiveness with a sensitivity of 90% and specificity of 100%. SVC collapsibility index was calculated as the difference in the maximum diameter of the SVC at end-expiration and minimum diameter at end-inspiration divided by its maximum diameter at end-expiration and expressed as a percentage.

SVC is more reliable because it is surrounded by pleural rather than abdominal pressure. However, it can only be adequately visualized by TEE. Ultrasonography, particularly TEE, requires formal training and expertise, and is operator dependent. Most importantly both methods are only valid in mechanically ventilated patients who are deeply sedated or paralyzed, are receiving a tidal volume of ≥8 mL/kg PBW, and are in normal sinus rhythm. The respiratory pattern of a spontaneously breathing patient is variable and inconsistent, and it is physiologically incorrect to use either method in such patients. Lastly, although the use of respiratory variation in IVC diameter to predict preload responsiveness has not been studied in patients with intraabdominal hypertension (IAH), this method will probably be inaccurate in such patients and should not be used in them. Continuous monitoring is not feasible with either of these methods.

5. Respiratory Variation in Arterial Blood Pressure Waveform-Derived Variables

During spontaneous breathing the respiratory changes in pleural pressure can cause cyclic changes in stroke volume and pulse pressure. During inspiration venous return and right ventricular (RV) preload increase but the left ventricular (LV) preload and SV and arterial PP decrease, and during expiration the opposite occurs—venous return and RV preload decrease but the LV preload and SV, and arterial PP increase. This phenomenon is known as pulsus paradoxus

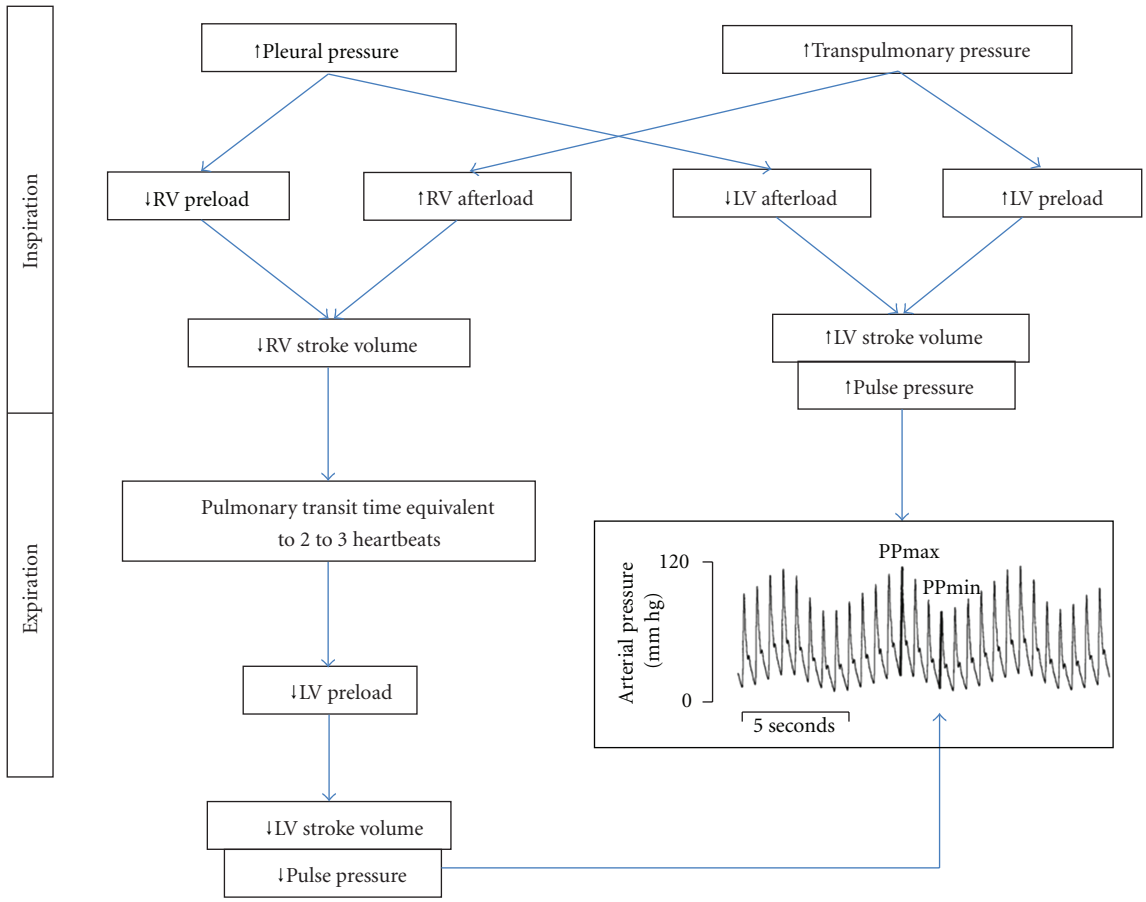


Figure 2: Phenomenon of reverse pulsus paradoxus. RV: right ventricular, LV: left ventricular, PP_{max}: maximum pulse pressure at end-inspiration, PP_{min}: minimum pulse pressure at end-expiration.

and is exaggerated when the two ventricles have to compete for space, for example, when there is pericardial tamponade or hyperinflation.

On the other hand, during mechanical ventilation the phenomenon is reversed; that is, during positive pressure inspiration venous return and RV preload decrease and RV afterload increases but the LV preload and SV, and arterial PP increase, and during expiration the opposite occurs (Figure 2). The decrease in venous return is due to the inspiratory increase in pleural pressure [17]. The increase in RV afterload is related to the inspiratory increase in transpulmonary pressure (alveolar minus pleural pressure) [18]. The decrease in RV preload and the increase in RV afterload both lead to a decrease in RV SV, which is therefore at its minimum at the end of the inspiratory period [19]. The inspiratory decrease in venous return is assumed to be the main mechanism of the inspiratory fall in RV SV [20]. On the other hand, the increase in LV preload leads to an increase in LV SV. The inspiratory decrease in RV SV leads to a decrease in LV preload after a phase lag of two-to-three heart beats because of the long transit time in the lungs [21]. Thus, the decrease in LV preload results in a decrease in LV SV, which is at its minimum during the expiratory period [19]. Two other mechanisms may also occur: positive pressure ventilation may induce a squeezing of blood out of alveolar vessels and thus transiently increase LV preload [22]; the inspiratory increase in pleural pressure may decrease LV afterload and thus facilitate LV ejection [23, 24]. This phenomenon of reverse pulsus paradoxus forms the basis for using respiratory variation in the arterial circulation to predict preload responsiveness. It will only be seen as long as the heart is still functioning on the ascending part of the Frank-Starling curve.

Pulse pressure variation (PPV) is calculated manually after measuring the maximum PP during inspiration and minimum PP during expiration from a 30 sec printout of the arterial BP waveform. The difference between the two PP readings is divided by the average of the two PP readings and expressed as a percentage.

Stroke volume variation (SVV) is calculated by a monitor (FloTrac Vigileo Edwards LifeSciences) that analyzes the arterial blood pressure waveform and uses a proprietary algorithm to convert PP in mmHg to SV in mL/heartbeat.

Numerous studies have shown that respiratory variation in either pulse pressure or stroke volume predicts preload responsiveness accurately. Marik et al. [7] performed a systematic review of 29 studies that included 685 patients and concluded that the mean threshold value, sensitivity,

and specificity for PPV were 12.5 ± 1.6%, 89%, and 88%, respectively, and the mean threshold value, sensitivity, and specificity for SVV were 11.6 ± 1.9%, 82%, and 86%, respectively.

Although both PPV and SVV predict preload responsiveness accurately, both are only valid in mechanically ventilated patients who are deeply sedated or paralyzed, receiving a tidal volume of ≥8 mL/kg PBW and in normal sinus rhythm because small tidal volumes and spontaneous breathing make the respiratory variation too small or unpredictable, and in the case of cardiac arrhythmia PPV and SVV are the result of altered ventricular filling, not respiratory variation [25]. Moreover, recent studies have revealed additional limitations: low heart rate/respiratory rate ratio (<3.6) [26], pulmonary hypertension and right ventricular systolic dysfunction [27–29], and norepinephrine [30]. This limits their usefulness in the general medical ICU patient population.

6. Respiratory Variation in Pulse Oximeter Plethysmographic Waveform-Derived Variables

The pulse oximeter plethysmographic (POP) waveform resembles the peripheral arterial waveform, and respiratory variation in the amplitude of the POP waveform can be used to predict preload responsiveness. It does not require an arterial line and therefore, is a noninvasive alternative.

Feissel et al. [31] used pulse oximeter plethysmography (Sonos 5500 Philips Medical Systems, Eindhoven, Netherlands) in 23 septic patients who were on mechanical ventilation, deeply sedated, receiving a tidal volume of ≥ 8 mL/kg PBW and in normal sinus rhythm, and showed the respiratory variation in the amplitude of the POP waveform; that is, ΔPplet of >14% was as accurate as a PPV of ≥13% in predicting preload responsiveness—defined as an increase in CI of ≥15% measured by TTE. However, calculation of the respiratory variation in the amplitude of the pulse oximeter plethysmographic waveform required sophisticated analysis on a computer.

Recently the development of plethysmographic variability index (PVI Massimo Corp.) has overcome the problem and allowed respiratory variation in the amplitude of the pulse oximeter plethysmographic waveform to be measured easily at the bedside or monitored continuously. PVI is a proprietary algorithm that allows for noninvasive, automated, continuous calculations of respiratory variation in pulse oximeter plethysmographic waveform using a pulse oximeter in mechanically ventilated patients. PVI is a measure of the dynamic change in perfusion index (PI)—the ratio of nonpulsatile to pulsatile blood flow through the peripheral capillary bed—occurring during a complete respiratory cycle [32].

Feissel et al. [33] used PVI in deeply sedated mechanically ventilated septic patients in normal sinus rhythm and showed that a value of >20 identified preload responsive patients with a sensitivity of 84% and specificity of 90%.

Loupec et al. [34] also showed that PVI can be used to predict preload responsiveness in deeply sedated mechanically ventilated surgical ICU patients in normal sinus rhythm.

Although PVI appears to be as accurate as PPV and SVV in predicting preload responsiveness, it too is only valid in mechanically ventilated patients who are deeply sedated or paralyzed, receiving a tidal volume of ≥8 mL/kg PBW, and in normal sinus rhythm. This limits its usefulness in the general medical ICU patient population. Moreover, it is not reliable if the peripheral perfusion is severely compromised.

7. Respiratory Variation in Aortic Blood Flow Velocity

Since Doppler US allows beat-to-beat measurement of blood velocity and blood velocity is proportional to LV stroke volume, the respiratory variation in peak aortic blood flow velocity, that is, ΔVpeak, can also be used to predict preload responsiveness.

Feissel et al. [35] used TEE in 19 ventilated patients with septic shock and normal LV systolic function and showed that a ΔVpeak of >12% predicted preload responsiveness with a sensitivity of 100% and specificity of 89%. ΔVpeak was calculated as the difference between maximum Vpeak and minimum Vpeak divided by the mean of the two values and expressed as a percentage.

Although an esophageal Doppler can be used instead of a TEE and can be left in place, it is also less reliable because the probe is inserted blindly, and the resulting waveform is highly dependent on correct positioning.

Limitations of both methods are similar to the ones that apply to PPV and SVV. Additional limitations precluding more widespread use are long learning curve with a lack of reproducibility, inability to obtain continuous reliable measurements, requirement for 24-hour availability, and practical problems related to the presence of the probe in the patient's esophagus [36].

8. Respiratory Variation in Brachial Artery Blood Flow Velocity

Brennan et al. [37] trained internal medicine residents to use a hand-carried US device (SonoSite Titan; Bothell, WA) with a 5 MHz broadband linear array transducer weighing 7.7 lb in 30 deeply sedated patients mechanically ventilated with tidal volume of ≥8 mL/kg PBW to measure blood flow velocity in the brachial artery and showed that ΔVpeak-BA of >16% predicted radial arterial PPV of ≥13% with a sensitivity of 91% and specificity of 95%. ΔVpeak-BA was calculated as the difference between maximum Vpeak and minimum Vpeak divided by the mean of the two values and expressed as a percentage.

The hand-carried US Doppler assessment of the ΔV peak-BA is a rapid, noninvasive bedside correlate to PPV but suffers from the same limitations; that is, it is only valid in mechanically ventilated patients who are deeply sedated or paralyzed, receiving a tidal volume of at least 8 ml/kg PBW and in normal sinus rhythm.

Table 2: Different methods of measuring CO or arterial blood flow velocity* during PLR maneuver.

Invasive	Semi-invasive	Noninvasive
Thermodilution	*US*	*US*
PAC (transpulmonary thermodilution)	*Esophageal Doppler	Transthoracic echocardiography
PiCCO (aortic transpulmonary thermodilution)		Transthoracic USCOM
Arterial BP waveform analysis		*Femoral arterial Doppler
FloTrac Vigileo		*Bioreactance*
		NICOM

CO: cardiac output, PLR: passive leg raising, PAC: pulmonary artery catheter, *US*: ultrasound, USCOM: ultrasonic cardiac output monitor, NICOM: noninvasive cardiac output monitor.

9. Electrical Impedance Tomography

This recently developed technology is another noninvasive method of measuring SVV. Electrical impedance tomography (EIT) measures changes in bioimpedance at skin electrodes to reconstruct sequences of cross-sectional functional images [38]. However, at the surface of the chest, 90% of the signal amplitude is due to breathing, and, thus, it becomes challenging to exploit the small respiratory variations in SV, which represent only 1% to 2% of the total signal strength. Conventional EIT postprocessing techniques are unable to analyze such low-amplitude events. Therefore, Maisch et al. [39] developed a novel method to determine SVV in the descending aorta by analyzing sequences of EIT images in the frequency domain (SVV_{EIT}) and tested it in an animal study. A wide range of hemodynamic conditions were induced in 8 pigs by mechanical ventilation at different levels of positive endexpiratory pressure (0–15 cm H_2O) and with tidal volumes of 8 and 16 mL/kg of body weight and by hypovolemia due to blood withdrawal with subsequent retransfusion followed by infusions of hydroxyethyl starch. Aortic SVV measured by EIT and compared to SVV derived from an aortic ultrasonic flow probe and from arterial pulse contour analysis showed significant correlation ($r^2 = 0.69$; $P < 0.001$, and $r^2 = 0.73$; $P < 0.001$, resp.) [39]. EIT appears to be a promising new noninvasive method of determining preload responsiveness; however, it has not been studied in humans yet.

10. Passive Leg Raising Maneuver

Raising the legs to 45 degrees from the supine or semirecumbent position mobilizes the reservoir of blood in the legs and the splanchnic circulation towards the chest and results in an endogenous volume challenge. If the heart is preload responsive, that is, it is functioning on the ascending portion of the Frank-Starling curve, PLR maneuver will result in an increase in CI within one minute. On the other hand, if the heart is not preload responsive, that is, it is functioning on the plateau part of the Frank-Starling curve, PLR will not result in an increase in CI [40].

The hemodynamic effect of PLR is similar to the intravenous infusion of fluids [41] and is not affected by the presence of spontaneous breathing. Moreover, since the mean change in CO after PLR is measured over several heartbeats, it is not affected by cardiac arrhythmias. Lastly, the hemodynamic effect is reversible.

A recent meta-analysis [10], which pooled the results of nine studies and included a total of 353 patients, confirmed the accuracy of the PLR maneuver in predicting preload responsiveness with a pooled sensitivity and specificity of 89.4% (84.1–93.4%) and 91.4% (85.9–95.2%), respectively. The pooled area under the receiver operating characteristics curve (AUC) was 0.95 (0.92–0.97) (Table 1).

Although Jabot et al. [42] found significant difference in hemodynamic response to PLR performed by starting from supine versus semirecumbent position, the meta-analysis (10) did not show any significant difference.

Moreover, the PLR maneuver cannot accurately predict preload responsiveness in patients with intra-abdominal hypertension (IAH) because venous return is impaired in such patients [43].

Most importantly, although the PLR maneuver is comparable in accuracy to PPV and SVV in predicting preload responsiveness (Table 1) and has the advantage of not being affected by the mode of breathing, tidal volume, or cardiac rhythm and therefore can be used in patients who are breathing spontaneously or have arrhythmias, and unlike an actual fluid challenge has no adverse effects, it requires measurement of SV (or CO) or alternatively a surrogate, for example, arterial blood flow velocity or PP.

Different methods of SV (or CO) measurement have been validated with the PLR maneuver, that is, PAC with continuous CO (cCO) monitoring capability using thermodilution technique [44], PiCCO thermodilution technique [45], FloTrac Vigileo [46], TTE [47, 48], transthoracic Doppler US (USCOM, Sydney, Australia) [49], or NICOM [50, 51]. Measurement of arterial blood flow velocity as a surrogate for SV (or CO) has also been validated with the PLR maneuver, that is, aortic blood flow velocity measured by esophageal Doppler US [52, 53] or femoral artery blood flow velocity measured by Doppler US [54] (Table 2).

The meta-analysis [10] also showed that the accuracy of the PLR maneuver is independent of the method used to measure the SV (or CO) or arterial blood flow velocity—PAC with cCO, PiCCO, FloTrac Vigileo, echocardiography, Doppler US. Of note, however, the studies using NICOM were not included in the meta-analysis because they had not been published at the time of the meta-analysis.

On the other hand when PP is used as a surrogate for SV (or CO) the accuracy of the PLR maneuver is lower:

Table 3: Critical components of the fluid challenge and one example of their application in a hypothetical patient (MAP of 65 mmHg and a CVP of 12 mmHg; two possible types of response are presented) [63].

Example	example 1			example 2		
(1) Type of fluid: Ringer's lactate	Baseline	+10 mins	+20 mins	Baseline	+10 mins	+20 mins
(2) Rate of infusion: 500 mL/30 mins						
(3) Clinical end-points: MAP of 75 mmHg	MAP 65	MAP 70	*MAP 75*	MAP 65	MAP 67	MAP 60
(4) Pressure safety limits: CVP of 15 mmHg	CVP 12	CVP 13 Continue	CVP 14 Stop	CVP 12	CVP 14 Continue	*CVP 15* Stop
		Successful fluid challenge			*Unsuccessful fluid challenge*	

MAP: mean arterial pressure, CVP: central venous pressure, mins: minutes [63].

pooled sensitivity of 59.5% (47.4–70.7%), specificity of 86.2% (75.3–93.5%), and AUC of 0.76 (0.67–0.86). This is because PP is not a direct measure of SV and is affected by the compliance of the vessel [10].

PAC with cCO monitoring capability using thermodilution technique, PiCCO, and FloTrac Vigileo are invasive and require a pulmonary artery catheter, both an internal jugular (IJ) or subclavian (SC) central venous line (CVL) and a femoral arterial line, and an arterial line, respectively, and, therefore, may not be feasible in the emergency room or on the floor during the initial resuscitation of sepsis. Moreover, unlike FloTrac Vigileo, PiCCO requires frequent recalibration. On the other hand, US techniques are non- or semi-invasive but require formal training and are operator dependent, and some like TTE or TEE are not continuous. Although an esophageal Doppler can be used instead of a TEE and can be left in place, it is also less reliable because the probe is inserted blindly, and the resulting waveform is highly dependent on correct positioning. Additional limitations precluding more widespread use are long learning curve with a lack of reproducibility, inability to obtain continuous reliable measurements, requirement for 24 hour availability, and practical problems related to the presence of the probe in the patient's esophagus [36].

USCOM and NICOM are two promising new technologies that measure CO non-invasively.

USCOM (Uscom Ltd., Sydney, Australia) is a transthoracic ultrasonic CO monitor that uses continuous wave Doppler technique to measure CO and has been validated with the PLR maneuver in critically ill patients. Thiel et al. [49] studied 89 medical ICU patients requiring volume expansion and found that a PLR-induced increase in SV ≥15% predicted preload responsiveness with a sensitivity of 81%, specificity of 93%, negative predictive value of 85%, and positive predictive value of 91%.

NICOM (Cheetah Medical, Washington, WA, USA) is a noninvasive CO monitor that is based on bioreactance technique and is comparable in accuracy to the invasive techniques of thermodilution (PAC with cCO, PiCCO) and arterial BP waveform analysis (FloTrac Vigileo) [55–59]. It consists of a 75 kHz sine wave generator and four dual electrode stickers that are used to establish electrical contact with the body. Measurement of CO is based on analysis of relative phase shifts of an oscillating current that occurs when this current traverses the thoracic cavity [60].

NICOM has been validated with the PLR maneuver in critically ill patients and shown acceptable accuracy [50, 51]. Lamia et al. [50] studied 11 hemodynamically unstable patients with spontaneously breathing activity in a respiratory critical care unit and found that a PLR-induced increase in SV of ≥9% predicted an increase in SV of ≥15% after a 500 mL NS bolus with a sensitivity of 100% and a specificity of 80%. Benomar et al. [51] studied 75 postcardiac surgery patients and found that PLR-induced increase in CO of ≥9% predicted an increase in CO of ≥9% after a 500 mL colloid bolus with a sensitivity of 68% and specificity of 95%.

Lakhal et al. [61] showed that combining the PLR maneuver with CVP can improve its accuracy since a ≥2 mmHg increase in CVP in a nonresponsive patient indicates that PLR guaranteed an adequate endogenous volume challenge.

11. Actual Fluid Challenge

Several decades ago, Weil and Henning [62] proposed the fluid challenge technique, based on the "2–5 rule" using the CVP and the "3–7 rule" for the PAWP. CVP was measured at 10 min intervals. If the change in CVP was <2 mmHg, the infusion was continued. If it was in the 2–5 mmHg range, the infusion was held and CVP remeasured after 10 min. If the change was an increase of >5 mmHg, the infusion was stopped. PAWP was used in a similar manner but with different cut-offs, that is, <3 mmHg, 3–7 mmHg, and >7 mmHg.

Recently Vincent and Weill [63] proposed a modified fluid challenge technique that incorporates 4 decisions phases: type of fluid, rate of administration, clinical end-points and pressure safety limits. Clinical end-points are usually correction of the hemodynamic abnormality that prompted the need for fluid, that is, hypotension, tachycardia, or oliguria. Although this technique like the one mentioned previously ("2–5" rule and "3–7" rule) has not been validated either, it appears to offer several advantages: quantitative goals together with limits are imposed, fluid deficits are more rapidly corrected, and fears of large volumes are minimized. Moreover, the protocol identifies cardiac failure early, based on early increases in filling pressures to threshold levels, and directs the clinician to search for causes of perfusion failure other than hypovolemia. See Table 3 for two illustrative examples of the technique.

It is important to realize that a fluid challenge technique that uses SV (or CO) or its surrogate as the end-point is the most accurate way of performing a fluid challenge maneuver and has been used as the gold standard for comparison in studies of the PLR maneuver to predict

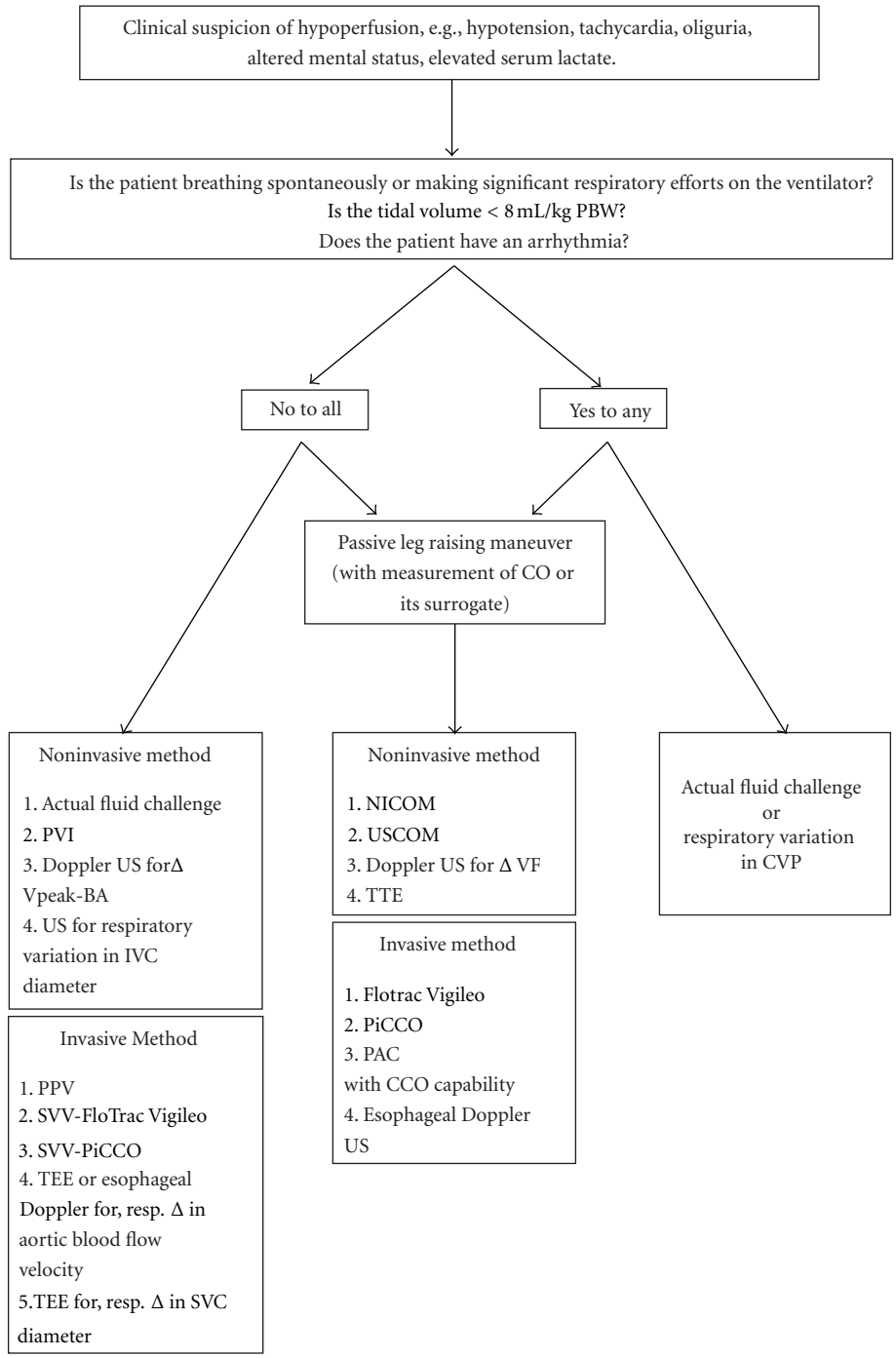


Figure 3: Approach to optimizing preload. PBW: predicted body weight, CO: cardiac output, PVI: pleth variability index, Δ*V*peak-BA: respiratory variation in peak brachial arterial blood flow velocity, US: ultrasonography, IVC: inferior vena cava, PPV: pulse pressure variation, SVV: stroke volume variation, TEE: transesophageal echocardiography, SVC: superior vena cava, NICOM: noninvasive cardiac output monitor, USCOM: ultrasonic cardiac output monitor, ΔVF: change in femoral artery blood flow velocity, CCO: continuous cardiac output, TTE: transthoracic echocardiography, PAC: pulmonary artery catheter, CVP: central venous pressure.

preload responsiveness. An increase in SV (or CO) ≥ of 15% defines preload responsiveness [10]. However, the requirement for measurement of SV (or CO) or alternatively a surrogate, for example, arterial blood flow velocity or pulse pressure, makes the fluid challenge maneuver that uses SV (or CO) or its surrogate as the end-point a more complex maneuver than the usual fluid challenge that uses other albeit less accurate end-points that is, BP, HR, and urine output.

An actual fluid challenge maneuver may not be appropriate in some clinical situations where an intravenous fluid

Table 4: Advantages and disadvantages of the various dynamic parameters used to predict preload responsiveness.

Method	Advantages	Disadvantages
Respiratory changes in CVP	Most critically ill septic patients have an IJ or SC CVL	It requires that the inspiratory effort be significant—a fall in PAWP of ≥2 mmHg was used in the original study by Magder et al. [11]
	It can be used in spontaneously breathing patients	
Respiratory changes in IVC diameter	It is non-invasive and requires an ultrasound with M-mode which is now becoming widely available	It is only reliable in mechanically ventilated patients who are receiving ≥8 mL/kg PBW tidal volume, are not making any significant respiratory efforts, and are in NSR
	It is easy to learn and teach	It may not be reliable in conditions associated with IAH, for example, obesity, massive ascites, abdominal compartment syndrome
	It can be easily repeated as often as necessary	
Respiratory changes in SVC diameter	It is more accurate than respiratory change in IVC diameter	It is semi-invasive and requires TEE and expertise in using it
		It is not continuous
		It too is only reliable in mechanically ventilated patients who are receiving ≥8 mL/kg PBW tidal volume, are not making any significant respiratory efforts, and are in NSR
PPV	PPV can be calculated manually from a 30 sec printout of the arterial blood pressure waveform	It is invasive and requires an arterial line
		It is only reliable in mechanically ventilated patients who are receiving ≥8 mL/kg PBW tidal volume, are not making any significant respiratory efforts, and are in NSR
SVV-FloTrac Vigileo	It does not require frequent recalibration	It is invasive and requires an arterial line
	It provides additional data: SV, CO	It is only reliable in mechanically ventilated patients who are receiving ≥8 mL/kg PBW tidal volume, are not making any significant respiratory efforts, and are in NSR
SVV-PiCCO Plus	It provides additional data: SV, CO, TBV, and EVLW	It is invasive and requires an IJ or SC CVL and a femoral arterial line with a thermistor
		It requires frequent recalibration
		It is only reliable in mechanically ventilated patients who are receiving ≥8 mL/kg PBW tidal volume, are not making any significant respiratory efforts, and are in NSR
PVI	It is noninvasive	It is only reliable in mechanically ventilated patients who are receiving ≥8 mL/kg PBW tidal volume, are not making any significant respiratory efforts, and are in NSR
	It is easy to use	It is not reliable if peripheral perfusion is severely compromised
	It does not require calibration	
Respiratory changes in aortic blood flow velocity	Esophageal Doppler US monitoring uses a smaller esophageal probe than TEE and therefore is less invasive; it can also be left in place for continuous monitoring; it also requires less training to use and is less expensive	Semi-invasive and requires TEE or esophageal Doppler US and expertise in using it
		It is only reliable in mechanically ventilated patients who are receiving ≥8 mL/kg PBW tidal volume, are not making any significant respiratory efforts, and are in NSR
		It suffers from additional limitations:
		Long learning curve with a lack of reproducibility

Table 4: Continued.

Method	Advantages	Disadvantages
		Inability to obtain continuous reliable measurements
		Requirement for 24-hour availability
		Practical problems related to the presence of the probe in the patient's esophagus
		As esophageal Doppler probes are inserted blindly, the resulting waveform is highly dependent on correct positioning
Respiratory changes in brachial artery blood flow velocity	It is non-invasive and requires only a US with Doppler which is now becoming widely available in ICUs	It is only reliable in mechanically ventilated patients who are receiving ≥8 mL/kg PBW tidal volume, are not making any significant respiratory efforts, and are in NSR
	It is easy to learn and teach as demonstrated by a study where residents used it after learning the technique	
PLR maneuver	It can be used in spontaneously breathing patients	It requires continuous CO monitoring by a technology with a rapid response time, for example, USCOM, NICOM, FloTrac Vigileo, PiCCO, or PAC with such capability
	It can be used in patients with arrhythmias	
	It can be completely noninvasive if CO is measured by a noninvasive method, for example, USCOM or NICOM	

CVP: central venous pressure, IJ: internal jugular, SC: subclavian, CVL: central venous line, PAWP: pulmonary artery wedge pressure, IVC: inferior vena cava, PBW: predicted body weight, NSR: normal sinus rhythm, IAH: intra-abdominal hypertension, SVC: superior vena cava, TEE: transesophageal echocardiography, PPV: pulse pressure variation, SVV: stroke volume variation, SV: stroke volume, CO: cardiac output, TBV: thoracic blood volume, EVLW: extravascular lung water, US: ultrasound, USCOM: ultrasonic cardiac output monitor, NICOM: noninvasive cardiac output monitor.

bolus may prove harmful, for example, severe acute respiratory distress syndrome (ARDS) or anuric acute tubular necrosis (ATN).

12. Summary of the Approach to Optimizing Preload

The choice of the method used to determine preload responsiveness depends upon patient-related factors as well as the available technology and expertise. The most important patient-related factors are mode of breathing (spontaneous versus deeply sedated or paralyzed on mechanical ventilation), tidal volume (< or ≥8 ml/kg PBW), and cardiac rhythm (normal sinus rhythm versus arrhythmia) (Figure 3, Table 4). Other factors that need to be considered are risks associated with the method, for example, PAC with cCO monitoring capability using thermodilution technique; PiCCO and FloTrac Vigileo which require a pulmonary artery catheter, both an IJ or SC CVL and a femoral arterial line, and an arterial line, respectively, are invasive and associated with risks of bleeding and infection which become even more important in critically ill septic patients particularly those with coagulopathy or neutropenia (Table 5). Noninvasive methods, therefore, present a very appealing alternative. Moreover, non-invasive methods like PVI and NICOM are faster compared to placing a CVL or arterial line which can be time consuming. Last but not least is the cost of technology. Although it appears that US may be an expensive tool to determine preload responsiveness, it is important to keep in mind that a US machine being reusable pays for itself in the long run. Similarly, other technologies that seem expensive are also fairly cost-effective when it is realized that the monitor (e.g., FloTrac Vigileo, PVI, NICOM) or device which is the main expense is a onetime investment and any disposable accessories (e.g., FloTrac sensors, finger sensors for PVI, NICOM electrode cables) are cheap (Table 6).

A PLR maneuver or actual fluid challenge combined with measurement of SV (or CO) or its surrogate is the best method to accurately predict preload responsiveness regardless of the mode of breathing, tidal volume, and cardiac rhythm.

If the patient is deeply sedated or paralyzed on a ventilator, is receiving a tidal volume of ≥8 mL/kg PBW, and is in normal sinus rhythm, "dynamic" parameters based on respiratory variation in the venous or arterial circulation, that is, IVC or SVC diameter, PPV, SVV, ΔPleth, PVI, aortic or brachial artery blood flow velocity, can accurately predict preload responsiveness. However, such a situation is commonly seen only in patients under general anesthesia in the operating room setting, and in fact most of the original studies using PPV and SVV were performed in such a setting.

On the other hand, most of the ICU patients are breathing spontaneously or making significant respiratory efforts on the ventilator. Under such circumstances, there are four options:

(1) PLR maneuver or actual fluid challenge maneuver combined with measurement of SV (or CO) or its surrogate,

(2) use of respiratory variation in CVP,

(3) the fluid challenge technique proposed by Vincent and Weil [63].

Both PLR maneuver and actual fluid challenge maneuver combined with measurement of SV (or CO) or its surrogate

Table 5: Complications of vascular catheters.

Immediate	Delayed
Central venous catheter and pulmonary artery catheters	
Bleeding	Infection
Retroperitoneal hematoma (with femoral approach)	Venous thrombosis, pulmonary emboli
Arterial puncture	Catheter migration
Arrhythmia	Catheter embolization
Air embolism	Myocardial perforation
Thoracic duct injury (with left SC or left IJ approach)	Nerve injury
Catheter malposition	
Pneumothorax or hemothorax	
Arterial catheters	
Bleeding	Infection
Retroperitoneal hematoma (with femoral approach)	Thrombosis
	Limb ischemia
	Cerebral embolization
	Nerve injury
	Pseudoaneurysm
	Arteriovenous fistula

IJ: internal jugular, SC: subclavian.

Table 6: Comparison of the cost of various technologies*.

	Cost of the equipment	Cost of the consumables
Flotrac Vigileo	EV1000 Clinical Platform: Placed (£0) to £14,450 Vigileo Monitor: Placed (£0) to £6,985	FloTrac sensors: £85–130 dependent upon volume/commitment
PVI	£1995	Finger sensor costs £8 per patient
Esophageal Doppler (CARDIOQ-ODM) for 6, 12, 24, 72, 240 hour use	£12,000	A range of probes is available ranging from £73–£96. Additionally, longer duration probes are available ranging from £116–£128
USCOM	£16,000	No consumables required
NICOM	£4995	Disposable patient sensors. Cost varies depending on quantity—if 200 bought, then cost is £40 per patient

*Information in this table obtained from the UK NHS Technology Adoption Centre's adoption pack 2012. http://www.ntac.nhs.uk/web/FILES/IOFM_Adoption_pack_final_080512.pdf.

require continuous real-time measurement of SV (or CO), that is, PAC with cCO, PiCCO, FloTrac Vigileo, USCOM or, NICOM, or alternatively, its surrogate, that is, aortic blood flow velocity measured by esophageal Doppler US or femoral artery blood flow velocity measured by Doppler US. Moreover, a PLR maneuver cannot be used in patients with IAH or pelvic fractures.

Use of respiratory variation in CVP to predict preload responsiveness requires that the inspiratory effort be significant enough to cause a 2 mmHg drop in PAWP, and therefore in the absence of a PAC to confirm such a significant respiratory effort the technique becomes subjective and dependent on observing the patient. Moreover, in a patient who is using expiratory abdominal muscles the release of abdominal muscle contraction may be confused for an inspiratory fall in CVP.

An actual fluid challenge maneuver may not be appropriate in some clinical situations where an intravenous fluid bolus may prove harmful, for example, severe ARDS or anuric ATN.

(4) Lastly, it is important to keep in mind that the "dynamic" parameters based on respiratory variation in the venous or arterial circulation, that is, IVC or SVC diameter, PPV, SVV, ΔPleth, PVI, aortic or brachial artery blood flow velocity, can still be used to predict preload responsiveness in a ventilated patient *if* the ventilated patient is *temporarily*

paralyzed and tidal volume is *temporarily* increased for a couple of minutes to 8–10 mL/kg PBW (unless contraindicated). Although they still cannot be used when the cardiac rhythm is irregular, the recent development of a new algorithm (SVVxtra Edwards Lifesciences, Irvine, CA, USA) *might* allow SVV to be used even *if* the cardiac rhythm is irregular. The new SVV algorithm is designed to restore the respiratory component of the arterial blood pressure waveform despite multiple ectopic heart beats. In a recent animal study Canneson et al. [64] used this new algorithm in 8 anesthetized and mechanically ventilated pigs. Multiple extrasystoles were induced by right ventricular pacing (25% of heart beats). Arterial blood pressure waveforms were recorded, and SVV was computed from the new and from the standard algorithm. A positive response to a bolus of 7 mL/kg of 6% hydroxy ethyl starch was defined as >15% increase in CO. The new SVV was higher in responders than in nonresponders (19 ± 5% versus 12 ± 3%, $P < 0.05$), whereas the standard SVV was similar in the two groups (29 ± 8% versus 26 ± 11%, $P = 0.4$). Receiver operating characteristic curve analysis showed that the new SVV was an accurate predictor of preload responsiveness (sensitivity = 86%, specificity = 85%, best cutoff value = 14%, AUC = 0.892 ± 0.052), whereas the standard SVV was not (AUC = 0.596 ± 0.077) [64].

Conflict of Interests

None of the authors has any conflict of interests with the content of this paper.

References

[1] C. V. Murphy, G. E. Schramm, J. A. Doherty et al., "The importance of fluid management in acute lung injury secondary to septic shock," *Chest*, vol. 136, no. 1, pp. 102–109, 2009.

[2] J. H. Boyd, J. Forbes, T. A. Nakada, K. R. Walley, and J. A. Russell, "Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality," *Critical Care Medicine*, vol. 39, no. 2, pp. 259–265, 2011.

[3] F. Alsous, M. Khamiees, A. DeGirolamo, Y. Amoateng-Adjepong, and C. A. Manthous, "Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study," *Chest*, vol. 117, no. 6, pp. 1749–1754, 2000.

[4] J. L. Vincent, Y. Sakr, C. L. Sprung et al., "Sepsis in European intensive care units: results of the SOAP study," *Critical Care Medicine*, vol. 34, no. 2, pp. 344–353, 2006.

[5] H. P. Wiedemann, A. P. Wheeler, G. R. Bernard et al., "Comparison of two fluid-management strategies in acute lung injury," *The New England Journal of Medicine*, vol. 354, no. 24, pp. 2564–2575, 2006.

[6] A. Vieillard-Baron, V. Caille, C. Charron, G. Belliard, B. Page, and F. Jardin, "Actual incidence of global left ventricular hypokinesia in adult septic shock," *Critical Care Medicine*, vol. 36, no. 6, pp. 1701–1706, 2008.

[7] P. E. Marik, R. Cavallazzi, T. Vasu, and A. Hirani, "Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature," *Critical Care Medicine*, vol. 37, no. 9, pp. 2642–2647, 2009.

[8] P. E. Marik, M. Baram, and B. Vahid, "Does central venous pressure predict fluid responsiveness?" *Chest*, vol. 134, no. 1, pp. 172–178, 2008.

[9] F. Michard and J. L. Teboul, "Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence," *Chest*, vol. 121, no. 6, pp. 2000–2008, 2002.

[10] F. Cavallaro, C. Sandroni, C. Marano et al., "Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies," *Intensive Care Medicine*, vol. 36, no. 9, pp. 1475–1483, 2010.

[11] S. Magder, G. Georgiadis, and T. Cheong, "Respiratory variations in right atrial pressure predict the response to fluid challenge," *Journal of Critical Care*, vol. 7, no. 2, pp. 76–85, 1992.

[12] S. Magder, "Fluid status and fluid responsiveness," *Current Opinion in Critical Care*, vol. 16, no. 4, pp. 289–296, 2010.

[13] P. Vignon, "Evaluation of fluid responsiveness in ventilated septic patients: back to venous return," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1699–1701, 2004.

[14] C. Barbier, Y. Loubières, C. Schmit et al., "Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1740–1746, 2004.

[15] M. Feissel, F. Michard, J. P. Faller, and J. L. Teboul, "The respiratory variation in inferior vena cava diameter as a guide to fluid therapy," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1834–1837, 2004.

[16] A. Vieillard-Baron, K. Chergui, A. Rabiller et al., "Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1734–1739, 2004.

[17] B. C. Morgan, W. E. Martin, T. F. Hornbein, E. W. Crawford, and W. G. Guntheroth, "Hemodynamic effects of intermittent positive pressure respiration," *Anesthesiology*, vol. 27, no. 5, pp. 584–590, 1966.

[18] S. Permutt, R. A. Wise, and R. G. Brower, "How changes in pleural and alveolar pressure cause changes in afterload and preload," in *Heart-Lung Interactions in Health and Disease*, S. M. Scharf and and S. S. Cassidy, Eds., pp. 243–250, Marcel Dekker, New York, NY, USA, 1989.

[19] F. Jardin, J. C. Farcot, and P. Gueret, "Cyclic changes in arterial pulse during respiratory support," *Circulation*, vol. 68, no. 2, pp. 266–274, 1983.

[20] H. Theres, J. Binkau, M. Laule et al., "Phase-related changes in right ventricular cardiac output under volume- controlled mechanical ventilation with positive end-expiratory pressure," *Critical Care Medicine*, vol. 27, no. 5, pp. 953–958, 1999.

[21] S. M. Scharf, R. Brown, N. Saunders, and L. H. Green, "Hemodynamic effects of positive-pressure inflation," *Journal of Applied Physiology Respiratory Environmental and Exercise Physiology*, vol. 49, no. 1, pp. 124–131, 1980.

[22] R. Brower, R. A. Wise, and C. Hassapoyannes, "Effect of lung inflation on lung blood volume and pulmonary venous flow," *Journal of Applied Physiology*, vol. 58, no. 3, pp. 954–963, 1985.

[23] M. R. Pinsky, G. M. Matuschak, and M. Klain, "Determinants of cardiac augmentation by elevations in intrathoracic pressure," *Journal of Applied Physiology*, vol. 58, no. 4, pp. 1189–1198, 1985.

[24] H. E. Fessler, R. G. Brower, R. A. Wise, and S. Permutt, "Mechanism of reduced LV afterload by systolic and diastolic positive pleural pressure," *Journal of Applied Physiology*, vol. 65, no. 3, pp. 1244–1250, 1988.

[25] F. Michard, "Changes in arterial pressure during mechanical ventilation," *Anesthesiology*, vol. 103, no. 2, pp. 419–428, 2005.

[26] D. De Backer, F. S. Taccone, R. Holsten, F. Ibrahimi, and J. L. Vincent, "Influence of respiratory rate on stroke volume variation in mechanically ventilated patients," *Anesthesiology*, vol. 110, no. 5, pp. 1092–1097, 2009.

[27] M. Wyler von Ballmoos, J. Takala, M. Roeck et al., "Pulse-pressure variation and hemodynamic response in patients with elevated pulmonary artery pressure: a clinical study," *Critical Care*, vol. 14, no. 3, article R111, 2010.

[28] F. Daudel, D. Tüller, S. Krähenbühl, S. M. Jakob, and J. Takala, "Pulse pressure variation and volume responsiveness during acutely increased pulmonary artery pressure: an experimental study," *Critical Care*, vol. 14, no. 3, article R122, 2010.

[29] Y. Mahjoub, C. Pila, A. Friggeri et al., "Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle," *Critical Care Medicine*, vol. 37, no. 9, pp. 2570–2575, 2009.

[30] S. Nouira, S. Elatrous, S. Dimassi et al., "Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock," *Critical Care Medicine*, vol. 33, no. 10, pp. 2339–2343, 2005.

[31] M. Feissel, J. L. Teboul, P. Merlani, J. Badie, J. P. Faller, and K. Bendjelid, "Plethysmographic dynamic indices predict fluid responsiveness in septic ventilated patients," *Intensive Care Medicine*, vol. 33, no. 6, pp. 993–999, 2007.

[32] M. Cannesson, O. Desebbe, P. Rosamel et al., "Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre," *British Journal of Anaesthesia*, vol. 101, no. 2, pp. 200–206, 2008.

[33] M. Feissel, R. Kalakhy, J. Badie, G. Robles, J. Faller, and J. L. Teboul, "Plethysmography variability index: a new fluid responsiveness parameter," *Critical Care*, vol. 13, supplement 1, article P205, 2009.

[34] T. Loupec, H. Nanadoumgar, D. Frasca et al., "Pleth variability index predicts fluid responsiveness in critically ill patients," *Critical Care Medicine*, vol. 39, no. 2, pp. 294–299, 2011.

[35] M. Feissel, F. Michard, I. Mangin, O. Ruyer, J. P. Faller, and J. L. Teboul, "Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock," *Chest*, vol. 119, no. 3, pp. 867–873, 2001.

[36] P. E. Marik, "Techniques for assessment of intravascular Volume in critically ill patients," *Journal of Intensive Care Medicine*, vol. 24, no. 5, pp. 329–337, 2009.

[37] J. M. Brennan, J. E. A. Blair, C. Hampole et al., "Radial artery pulse pressure variation correlates with brachial artery peak velocity variation in ventilated subjects when measured by internal medicine residents using hand-carried ultrasound devices," *Chest*, vol. 131, no. 5, pp. 1301–1307, 2007.

[38] M. Bodenstein, M. David, and K. Markstaller, "Principles of electrical impedance tomography and its clinical application," *Critical Care Medicine*, vol. 37, no. 2, pp. 713–724, 2009.

[39] S. Maisch, S. H. Bohm, J. Solà et al., "Heart-lung interactions measured by electrical impedance tomography," *Critical Care Medicine*, vol. 39, pp. 2173–2176, 2011.

[40] X. Monnet and J. L. Teboul, "Passive leg raising," *Intensive Care Medicine*, vol. 34, no. 4, pp. 659–663, 2008.

[41] V. Caille, J. Jabot, G. Belliard, C. Charron, F. Jardin, and A. Vieillard-Baron, "Hemodynamic effects of passive leg raising: an echocardiographic study in patients with shock," *Intensive Care Medicine*, vol. 34, no. 7, pp. 1239–1245, 2008.

[42] J. Jabot, J. L. Teboul, C. Richard, and X. Monnet, "Passive leg raising for predicting fluid responsiveness: importance of the postural change," *Intensive Care Medicine*, vol. 35, no. 1, pp. 85–90, 2009.

[43] Y. Mahjoub, J. Touzeau, N. Airapetian et al., "The passive leg-raising maneuver cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension," *Critical Care Medicine*, vol. 38, no. 9, pp. 1824–1829, 2010.

[44] T. Boulain, J. M. Achard, J. L. Teboul, C. Richard, D. Perrotin, and G. Ginies, "Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients," *Chest*, vol. 121, no. 4, pp. 1245–1252, 2002.

[45] X. Monnet, D. Osman, C. Ridel, B. Lamia, C. Richard, and J. L. Teboul, "Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients," *Critical Care Medicine*, vol. 37, no. 3, pp. 951–956, 2009.

[46] M. Biais, L. Vidil, P. Sarrabay, V. Cottenceau, P. Revel, and F. Sztark, "Changes in stroke volume induced by passive leg raising in spontaneously breathing patients: comparison between echocardiography and Vigileo/FloTrac device," *Critical Care*, vol. 13, no. 6, article R195, 2009.

[47] B. Lamia, A. Ochagavia, X. Monnet, D. Chemla, C. Richard, and J. L. Teboul, "Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1125–1132, 2007.

[48] J. Maizel, N. Airapetian, E. Lorne, C. Tribouilloy, Z. Massy, and M. Slama, "Diagnosis of central hypovolemia by using passive leg raising," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1133–1138, 2007.

[49] S. W. Thiel, M. H. Kollef, and W. Isakow, "Non-invasive stroke volume measurement and passive leg raising predict volume responsiveness in medical ICU patients: an observational cohort study," *Critical Care*, vol. 13, no. 4, article R111, 2009.

[50] B. Lamia, A. Cuvelier, P. L. Declercq, L. C. Molano, M. R. Pinsky, and J. F. Muir, "Response of NICOM stroke volume to passive leg raising to predict fluid responsiveness in critically ill patients with spontaneous breathing activity," *Critical Care*, vol. 14, supplement 1, article P113, 2010.

[51] B. Benomar, A. Ouattara, P. Estagnasie, A. Brusset, and P. Squara, "Fluid responsiveness predicted by noninvasive bioreactance-based passive leg raise test," *Intensive Care Medicine*, vol. 36, no. 11, pp. 1875–1881, 2010.

[52] X. Monnet, M. Rienzo, D. Osman et al., "Passive leg raising predicts fluid responsiveness in the critically ill," *Critical Care Medicine*, vol. 34, no. 5, pp. 1402–1407, 2006.

[53] A. Lafanechère, F. Pène, C. Goulenok et al., "Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients," *Critical Care*, vol. 10, no. 5, article R32, 2006.

[54] S. Préau, F. Saulnier, F. Dewavrin, A. Durocher, and J. L. Chagnon, "Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis," *Critical Care Medicine*, vol. 38, no. 3, pp. 819–825, 2010.

[55] P. Squara, D. Denjean, P. Estagnasie, A. Brusset, J. C. Dib, and C. Dubois, "Noninvasive cardiac output monitoring (NICOM): a clinical validation," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1191–1194, 2007.

[56] S. Marqué, A. Cariou, J. D. Chiche, and P. Squara, "Comparison between Flotrac-Vigileo and Bioreactance, a totally noninvasive method for cardiac output monitoring," *Critical Care*, vol. 13, no. 3, article R73, 2009.

[57] D. Rotcajg, D. Denjean, P. Estagnasie, A. Brusset, and P. Squara, "Comparison of monitoring performance of Bioreactance vs. pulse contour during lung recruitment maneuvers," *Critical Care*, vol. 13, no. 4, article R125, 2009.

[58] N. Y. Raval, P. Squara, M. Cleman, K. Yalamanchili, M. Winklmaier, and D. Burkhoff, "Multicenter evaluation of noninvasive cardiac output measurement by bioreactance technique," *Journal of Clinical Monitoring and Computing*, vol. 22, no. 2, pp. 113–119, 2008.

[59] P. Squara, M. Cecconi, A. Rhodes, M. Singer, and J. D. Chiche, "Tracking changes in cardiac output: methodological considerations for the validation of monitoring devices," *Intensive Care Medicine*, vol. 35, no. 10, pp. 1801–1808, 2009.

[60] H. Keren, D. Burkhoff, and P. Squara, "Evaluation of a noninvasive continuous cardiac output monitoring system based on thoracic bioreactance," *American Journal of Physiology*, vol. 293, no. 1, pp. H583–H589, 2007.

[61] K. Lakhal, S. Ehrmann, I. Runge et al., "Central venous pressure measurements improve the accuracy of leg raising-induced change in pulse pressure to predict fluid responsiveness," *Intensive Care Medicine*, vol. 36, no. 6, pp. 940–948, 2010.

[62] M. H. Weil and R. J. Henning, "New concepts in the diagnosis and fluid treatment of circulatory shock," *Anesthesia and Analgesia*, vol. 58, no. 2, pp. 124–132, 1979.

[63] J. L. Vincent and M. H. Weil, "Fluid challenge revisited," *Critical Care Medicine*, vol. 34, no. 5, pp. 1333–1337, 2006.

[64] M. Cannesson, N. P. Tran, M. Cho, F. Hatib, and F. Michard, "Predicting fluid responsiveness with stroke volume variation despite multiple extrasystoles," *Critical Care Medicine*, vol. 40, no. 1, pp. 193–198, 2012.

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 687018, 8 pages
doi:10.1155/2012/687018

Research Article

Goal-Directed Fluid Therapy Using Stroke Volume Variation Does Not Result in Pulmonary Fluid Overload in Thoracic Surgery Requiring One-Lung Ventilation

Sebastian Haas,[1] Volker Eichhorn,[2] Ted Hasbach,[1] Constantin Trepte,[1] Asad Kutup,[3] Alwin E. Goetz,[1] and Daniel A. Reuter[1]

[1] *Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, Cardiovascular Research Center, University Medical Center Hamburg-Eppendorf, Martinistraβe 52, 20246 Hamburg, Germany*
[2] *Department of Anesthesiology and Intensive Care, Evangelisches Krankenhaus Mühlheim, 45468 Mühlheim, Germany*
[3] *Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany*

Correspondence should be addressed to Sebastian Haas, shaas@uke.de

Received 1 April 2012; Accepted 8 May 2012

Academic Editor: Lars J. Bjertnaes

Background. Goal-directed fluid therapy (GDT) guided by functional parameters of preload, such as stroke volume variation (SVV), seems to optimize hemodynamics and possibly improves clinical outcome. However, this strategy is believed to be rather fluid aggressive, and, furthermore, during surgery requiring thoracotomy, the ability of SVV to predict volume responsiveness has raised some controversy. So far it is not known whether GDT is associated with pulmonary fluid overload and a deleterious reduction in pulmonary function in thoracic surgery requiring one-lung-ventilation (OLV). Therefore, we assessed the perioperative course of extravascular lung water index (EVLWI) and p_aO_2/F_iO_2-ratio during and after thoracic surgery requiring lateral thoracotomy and OLV to evaluate the hypothesis that fluid therapy guided by SVV results in pulmonary fluid overload. *Methods*. A total of 27 patients (group T) were enrolled in this prospective study with 11 patients undergoing lung surgery (group L) and 16 patients undergoing esophagectomy (group E). Goal-directed fluid management was guided by SVV (SVV < 10%). Measurements were performed directly after induction of anesthesia (baseline—BL), 15 minutes after implementation OLV (OLVimpl15), and 15 minutes after termination of OLV (OLVterm15). In addition, postoperative measurements were performed at 6 (6postop), 12 (12postop), and 24 (24postop) hours after surgery. EVLWI was measured at all predefined steps. The p_aO_2/F_iO_2-ratio was determined at each point during mechanical ventilation (group L: BL-OLVterm15; group E: BL-24postop). *Results*. In all patients (group T), there was no significant change ($P > 0.05$) in EVLWI during the observation period (BL: 7.8 ± 2.5, 24postop: 8.1 ± 2.4 mL/kg). A subgroup analysis for group L and group E also did not reveal significant changes of EVLWI. The p_aO_2/F_iO_2-ratio decreased significantly during the observation period (group L: BL: 462 ± 140, OLVterm15: 338 ± 112 mmHg; group E: BL: 389 ± 101, 24postop: 303 ± 74 mmHg) but remained >300 mmHg except during OLV. *Conclusions*. SVV-guided fluid management in thoracic surgery requiring lateral thoracotomy and one-lung ventilation does not result in pulmonary fluid overload. Although oxygenation was reduced, pulmonary function remained within a clinically acceptable range.

1. Introduction

Early, preemptive strategies of hemodynamic optimization are an important factor for sufficient organ microcirculation and are considered to be associated with reduced morbidity and mortality [1]. Within this context, improvement of intravascular volume status seems essential. After central venous pressure (CVP) was identified as inappropriate for the assessment of intravascular volume status, volumetric and functional parameters of preload came into the focus of interest. Clinical studies were thus initiated to evaluate the potential of fluid management guided by these parameters. Although one study failed to demonstrate improvements, other studies have shown improvements in hemodynamics

leading to benefits in clinical outcome when goal-directed fluid therapy was guided by global enddiastolic volume (GEDV), pulse pressure variation (PPV), or stroke volume variation (SVV) [2–5]. However, in thoracic surgery, the potential benefit or even disadvantage of volume management guided by functional parameters of preload have not been evaluated thus far. One possible disadvantage may be the fact that fluid management guided by functional parameters of preload is suspected to be a rather fluid aggressive approach since in the clinical studies the goal-directed group received more fluids than the control group [2–5]. Lopes and colleagues reported a more than double amount of fluid administration in the PPV-guided fluid management group [4]. It hast to be kept in mind that pulmonary fluid overload has been identified as an independent risk factor for the development of perioperative acute lung injury after lung surgery [6]. Therefore, a volume restrictive regime is usually recommended for lung surgery [6–9].

The extravascular fluid content of the lungs can be quantified using transpulmonary thermodilution (TCPTD) by measuring the extravascular lung water index (EVLWI). EVLWI by thermodilution was identified as more sensitive for quantifying the fluid content of the lungs than chest radiographs [10–12]. Furthermore, EVLWI is known as a prognostic parameter for clinical outcome in critically ill patients [13–17].

Fluid management in thoracic surgery is of particular importance because of the influence of one-lung ventilation (OLV). It has been reported that OLV by itself can be a cause of postoperative pulmonary edema [17–20]. Edema formation after OLV is explained by oxidative stress during—and in particular immediately following—OLV by reexpansion of the deflated lung, once conventional ventilation is reestablished [19–22]. Therefore, OLV might act as an additional factor for aggravating a perioperative pulmonary fluid overload.

In open chest conditions, the use of functional parameters of preload such as SVV to predict volume responsiveness is controversial [23–28]. As this question is not conclusively answered, the feasibility of SVV-guided fluid management remains unclear.

The hypothesis of our study was that fluid management guided by SVV results in fluid overload of the lungs during and after thoracic surgery that requires lateral thoracotomy and OLV. Therefore, the aim of the study was to investigate the influence of SVV-guided fluid management on the perioperative course of the formation of pulmonary extravascular fluid content as measured by EVLWI (first endpoint) and gas exchange measured by p_aO_2/F_iO_2-ratio (second endpoint) in thoracic surgery requiring lateral thoracotomy and OLV. Furthermore, 30-day mortality was assessed.

2. Materials and Methods

Approval for this study was provided by the Ethics Committee of the Hamburg Medical Board (Aerztekammer Hamburg). All patients gave written informed consent.

2.1. Patients. A total of 27 patients (group T, $n = 27$) scheduled for elective thoracic surgery requiring OLV were enrolled in this prospective study. Exclusion criteria were age under 18 years, cardiac arrhythmias and/or atrial fibrillation, and the presence of contraindications to femoral arterial catheterization.

2.2. Anesthesia. All patients were premedicated with midazolam 0.1 mg/kg orally before arriving in the operating room. All patients received an epidural catheter at level Th4 to Th7. A bolus of 0.125 mL/kg of 0.5% bupivacaine and 10 μg sufentanil was administered followed by a continuous administration of 0.5% bupivacaine (0.05 mL/kg/h). After surgery, administration of bupivacaine was stopped and 0.2% ropivacaine was administered at an infusion rate of 8 mL/h and was adjusted to the clinical situation. Directly after placement of the epidural catheter, general anesthesia was induced with 0.7 μg/kg sufentanil, 2.5 mg/kg propofol, and 0.6–0.8 mg/kg rocuronium. Anesthesia was maintained with isoflurane 1–1.5% in oxygen and sufentanil, and rocuronium was used for further relaxation. During surgery, a dosage of 0.2-0.3 μg/kg sufentanil was administered every 45 minutes or when clinically required. Neuromuscular monitoring was used for further rocuronium application, and a dosage of 0.1-0.2 mg/kg rocuronium was repeated when the train of four (TOF) ratio was >0.5. A left-sided double-lumen tube (Broncho-Cath; 37–41 French, Mallinckrodt Medical Ltd, Ireland) was introduced and adjusted using a fiberoptic bronchoscope.

2.3. Ventilation. Ventilation was performed using pressure-controlled mode. During conventional ventilation of both lungs, pressure control was adjusted to achieve tidal volumes of 8 mL/kg. A positive end-expiratory pressure (PEEP) of 8 cm H_2O was selected. The inspiratory-expiratory ratio was 1 : 1.7. The respiratory rate was adjusted to maintain the arterial partial pressure of carbon dioxide between 36 and 44 mmHg. During OLV, the ventilation pattern was modified using a PEEP of 3 cm H_2O, and tidal volumes of 4–6 mL/kg. The inspired oxygen fraction was initially 1.0 and decreased to a level which allowed maintenance of $P_aO_2 > 80$ mmHg.

2.4. Hemodynamic Monitoring. A central venous line was placed into the internal jugular vein for the continuous monitoring of central venous pressure, drug administration and injection of cold indicator for thermodilution. A 5-Fr thermistor-tipped catheter (PICCO, PV2025L20, Pulsion Medical Systems AG, Munich, Germany) was inserted into the femoral artery and connected to a hemodynamic monitor (PiCCO plus, Pulsion Medical Systems AG, Munich, Germany) for continuous measurement of SVV, arterial pressure and intermittent assessment of cardiac index (CI), global enddiastolic volume index (GEDI), stroke volume index (SVI), and EVLWI by TCPTD. Thermodilution measurements were performed by three sequential central venous injections of 10 mL cold saline solution (<8°C). All thermodilution curves were examined, and measurements were

accepted if none of the three consecutive values differed by more than 10% from the mean.

2.5. Study Protocol. All patients received continuous infusion of crystalloid infusion (Sterofundin Ecoflac Plus, Braun AG, Melsung Germany) at a rate of 9 mL/kg/h intraoperatively. Continuous administration was reduced to 4 mL/kg/h after surgery and continuous administration was further reduced to 2 mL/kg/h after extubation. These rather high infusion rates were chosen to provide a rather fluid aggressive study protocol. 1000 mL Sterofundin content 5.5 g NaCl, 0.3 g KCl, 0.37 g $CaCl_2$, 0.2 g $MgCl_2$, and 0.05 g natrium-lactate. Osmolarity is 299 mOsm/L. Additionally, a bolus of 5 mL/kg colloid (Voluven 130/0.4 6%, Fresenius Kabi AG, Bad Homburg, Germany) was given when SVV was above 10% and repeated if necessary until SVV returned to below 10%. Colloid administration, in order to achieve an SVV of lower than 10% was primarily done prior to open-chest conditions and continued during the surgical phase with a laterally opened thoracic cavity and after surgery. If clinically indicated (according to the International Normalized Ratio (INR) > 1.6 in combination with active bleeding), the required fluid loading was done with fresh frozen plasma. When mean arterial pressure dropped below 60 mmHg despite fluid resuscitation or during sudden blood loss, continuous norepinephrine administration was initiated. After extubation, SVV-guided fluid management was discontinued because SVV is not validated for use during spontaneous breathing. Hemodynamic measurements as well as arterial blood gas analyses were performed after induction of anesthesia (baseline—BL), 20 min after implementation of OLV (OLVimpl15) and 15 min after termination of OLV (OLVterm15), as well as at 6 h (6postop), 12 h (12postop), and 24 h (24postop) after the end of surgery.

2.6. Surgical Procedures. In the 11 patients with lung surgery, lobectomy was performed in 9 patients and bi-lobectomy in 2 patients. In the esophageal surgery group all 16 patients underwent transthoracic esophagectomy with two-field lymphadenectomy and reconstruction achieved by gastric pull up. None of the patients received neoadjuvant treatment.

2.7. Extravascular Lung Water Index (EVLWI) and Pulmonary Function. EVLWI was measured by transpulmonary thermodilution for quantification of pulmonary extravascular fluid content. To evaluate pulmonary compliance, the static pulmonary compliance C [L/cmH_2O] was assessed using the equation $C = V/\Delta P$, where V is the tidal volume and ΔP is the difference of inspiration pressure and PEEP. Oxygenation was quantified by calculating the p_aO_2/F_iO_2-ratio (arterial partial pressure of oxygen p_aO_2/inspiratory oxygen concentration F_iO_2) for each patient at each point of measurement as long as the patient was intubated and mechanically ventilated (Group L: from BL to OLVterm15, Group E: from BL to 24postop).

2.8. Metabolic and Hemodynamic Parameters. Blood lactate, central venous oxygen saturation ($ScvO_2$), and base excess (BE) were assessed. Furthermore, hemodynamic data such as mean arterial pressure (AP_{mean}), central venous pressure (CVP), global enddiastolic volume index (GEDI), stroke volume index (SVI), cardiac index (CI), pulmonary compliance, and norepinephrine administration were recorded at the predefined steps BL-24postop to describe metabolic and hemodynamic consequences during and after SVV-guided fluid management in thoracic surgery requiring lateral thoracotomy and OLV.

2.9. Subgroup Analysis. To further evaluate our hypothesis, a subgroup analysis of two subgroups was performed. Firstly, the course of EVLWI was explored in the lung surgery (group L: $n = 11$). Lung surgery is usually associated with a relatively short period of OLV and direct trauma to the lungs. Secondly, the course of EVLWI was investigated in transthoracic esophagectomy (group E: $n = 16$), an intervention involving severe general surgical trauma, a longer period of OLV, and higher fluid turnover.

2.10. Statistical Analysis. Descriptive statistical analysis was performed using SigmaStat and SigmaPlot (Systat Software, Inc., Germany). Student t-test was performed for corresponding group comparison regarding patients characteristics and surgery data between group L and group E. Normally distributed data (Kolmogorov-Smirnov-Test) were analyzed with a Tukey's one-way analysis of variance for repeated measurements (ANOVA), nonnormally distributed parameters were analyzed with Kruskal-Wallis Analysis of Variance (ANOVA) on Ranks. Results are given as mean ± standard deviation (SD). A P value < 0.05 was considered statistically significant.

3. Results

Patient's characteristics and comorbidities are given in Table 1. Patients did not differ significantly regarding age, body mass index, and ASA classification. Data regarding surgery, fluid administration and diuresis are presented in Table 2. All parameters were significantly higher in group E than in group L ($P < 0.05$) apart from the duration of OLV ($P = 0.057$) and red blood cell administration ($P = 0.223$).

3.1. Extravascular Lung Water Index (EVLWI). In all patients (group T), EVLWI did not change significantly during the observation period (BL: 7.8 ± 2.5, 24postop: 8.1 ± 2.4 mL/kg). The course of EVLWI in the subgroup analysis (group L: BL: 7.9 ± 1.7 mL × kg^{-1}, 24postop: 7.2 ± 1.9 mL/kg; group E: BL: 7.8 ± 3 mL/kg, 24postop: 9.1 ± 2.5 mL/kg) also revealed no significant changes. The highest mean of EVLWI was measured in group E at 24postop (9.1 mL/kg).

3.2. P_aO_2/F_iO_2-Ratio. In all patients (group T), the p_aO_2/F_iO_2-ratio decreased when comparing values prior to (BL) and after OLV (OLVterm15) (BL: 419 ± 122 mmHg, OLVterm15: 334 ± 92 mmHg). In subgroup L, the p_aO_2/F_iO_2-ratio also decreased significantly from 462 ± 140 mmHg at BL to 338 ± 112 mmHg at OLVterm15. In group E, a decrease

Table 1: Patient's characteristics and comorbidities. Patients did not differ significantly ($P > 0.05$) between group L and group E regarding age, body mass index, and ASA classification.

	All patients ($n = 27$)	Group L ($n = 11$)	Group E ($n = 16$)	P value
Age [years]	61.3 ± 11.6	62.1 ± 10.6	60.4 ± 13.4	$P = 0.72$
Body mass index [kg/m^2]	25.4 ± 5.2	24.7 ± 5.5	26 ± 5.2	$P = 0.56$
ASA classification	2.7 ± 0.3	2.5 ± 0.3	2.8 ± 0.3	$P = 0.65$
Coronary artery disease	5	2	3	
Impaired ventricular function (EF < 40%)	3	1	2	
Renal insufficiency	4	2	2	
Chronic obstructive pulmonary disease	10	8	2	

Table 2: Surgical data, fluid administration, and diuresis. *Statistical significance between group L and group E analyzed by students t-test ($P < 0.05$).

	All patients ($n = 27$)	Group L ($n = 11$)	Group E ($n = 16$)	P value
Duration of surgery [min]	294.3 ± 144.4	177.5 ± 76.7	375.7 ± 123.6*	$P < 0.001$
Duration of OLV [min]	134.8 ± 25.6	113.3 ± 55.7	149.3 ± 39.3	$P = 0.057$
Blood loss during surgery [mL]	538 ± 784	190 ± 347	778 ± 914	$P = 0.037$
Number of patients received noradrenaline	22	6	16	
Crystalloid administered during observation period [mL/kg/h]	3.4 ± 0.8	2.8 ± 0.8	3.8 ± 0.8*	$P = 0.003$
Colloid administered during observation period [mL/kg/h]	1.2 ± 0.4	0.6 ± 0.3	1.5 ± 0.5*	$P < 0.001$
Fresh frozen plasma administered during observation period [mL]	514 ± 840	0	770 ± 933*	$P = 0.012$
Packed red blood cells administered during observation period [mL]	545 ± 697	320 ± 345.1	640 ± 642	$P = 0.223$
Diuresis [mL/kg/h]	1.3 ± 0.4	0.9 ± 0.3	1.6 ± 0.4*	$P < 0.001$

in the p_aO_2/F_iO_2-ratio was observed 24 hrs after surgery (BL 389 ± 101 mmHg, 24postop: 303 ± 74 mmHg). The lowest mean p_aO_2/F_iO_2-ratio was observed in group E except for during OLV at timepoint 24postop (303 ± 74 mmHg). Patients of group L were extubated immediately after the end of surgery, whereas patients of group E were extubated 24 h after the end of surgery.

3.3. Cardiac Index. CI was increased at timepoints OLVimpl15 and 6postop compared to baseline timepoint BL in all patients. (BL: 2.8 ± 0.9 L/min/m^2, OLVimpl15: 3.9 ± 0.9 L/min/m^2, 6postop: 3.5 ± 0.9 L/min/m^2). In the subgroup analysis, CI increased significantly at OLVimpl15 in group E (BL: 2.7 ± 0.9 L/min/m^2, OLVimpl15: 3.7 ± 1 L/min/m^2).

3.4. 30-Day Mortality. One patient in group L died due to malignoma-induced erosive bleeding of the pulmonary artery on the second day after surgery. One patient in group E died 28 days after surgery due to septic shock and severe mediastinitis. Thus, 30-day mortality was 7.4% for all patients, 9.1% in group L, and 6.3% in group E.

3.5. Metabolic Data. Lactate levels, central venous oxygen saturation ($ScvO_2$), base excess (BE), and hemoglobin (Hb) are given in Table 3. Lactate levels increased significantly at 6postop, 12postop, and 24postop in group T and group E compared to BL. However, levels of lactate remained very low (<1.4 mmol/L). $ScvO_2$ decreased significantly, in all groups at 12postop, and 24postop compared to BL, but always remained in a range above 70%. BE decreased significantly at 6postop, 12postop and 24postop compared to BL. Hb was also significantly reduced at most timepoints compared to BL. At this point it has to be clearly stated that all significant changes in all metabolic data were well within normal values and have to been seen clinically irrelevant.

In addition to EVLWI, p_aO_2/F_iO_2-ratio and CI, further data on hemodynamics (AP_{mean} [mmHg], CVP [mmHg], GEDI [mL/m^2]), SVI [mL/m^2], pulmonary compliance [L/cmH_2O], and norepinephrine administration [μg/kg/min] are shown in Table 4. In group L, 6 of 11 patients required norepinephrine administration temporarily; in group E, all patients required temporary norepinephrine administration.

4. Discussion

Although fluid management guided by functional parameters of preload are suggested to be rather fluid aggressive and validity of these parameters are controversial under open chest conditions, the present study shows that this goal-directed approach does not result in pulmonary fluid overload and deleterious reduction of pulmonary function in thoracic surgery requiring lateral thoracotomy and OLV. Furthermore, no derangement in metabolic parameters or increase in mortality associated with an altered pulmonary function could be identified. Whether this treatment strategy that demonstrated potential clinical benefit in abdominal and cardiac surgery is also potentially useful in this field

Table 3: Metabolic data. $ScvO_2$: central venous oxygen saturation; BE: base excess. *Difference to BL in analysis of variance (ANOVA) ($P < 0.05$). BL: directly after induction of anesthesia; OLVimpl15: 15 minutes after beginning OLV; OLVterm15: 15 minutes after cessation of OLV; 6postop: 6 hours after surgery; 12postop: 12 hours after surgery; 24postop: 24 hours after surgery.

	BL	OLVimpl15	OLVterm15	6postop	12postop	24postop
$Lactate_T$ [mmol/L]	0.8 ± 0.3	0.8 ± 0.2	1.1 ± 0.5	1.2* ± 0.6	1.1* ± 0.4	1.2* ± 0.4
$Lactate_L$ [mmol/L]	0.8 ± 0.4	0.7 ± 0.2	1 ± 0.5	0.9 ± 0.3	1 ± 0.4	1.1 ± 0.4
$Lactate_E$ [mmol/L]	0.8 ± 0.2	0.9 ± 0.2	1.2 ± 0.5	1.4 ± 0.6*	1.2 ± 0.4*	1.2 ± 0.3*
$ScvO_{2T}$ [%]	84.6 ± 6.5	85.7 ± 5.6	86.8 ± 4.8	76.9 ± 4.9*	72.7 ± 8.3*	72.6 ± 9.0*
$ScvO_{2L}$ [%]	87.0 ± 5.4	87.3 ± 4.9	87.5 ± 4.6	76.8 ± 4.9*	74.8 ± 2.9*	74.0 ± 6.7*
$ScvO_{2E}$ [%]	82.9 ± 6.7	84.6 ± 6.0	86.3 ± 5.1	77.0 ± 5.1	71.7 ± 10*	72.0 ± 10.1*
BE_T [mmol/L]	−2.5 ± 2.9	−5.1 ± 3.3*	−6.3 ± 3.3*	−5.5 ± 2.6*	−5.8 ± 2.1*	−5.5 ± 1.9*
BE_L [mmol/L]	−1.9 ± 2.9	−3.2 ± 2.6*	−4.5 ± 2.0*	−4.4 ± 1.8*	−4.7 ± 2.3*	−4.7 ± 2*
BE_E [mmol/L]	−2.9 ± 3.0	−6.3 ± 3.1*	−7.5 ± 3.5*	−6.3 ± 2.8*	−6.4 ± 1.9*	−5.8 ± 1.9
Hb_T [mg/dL]	10.5 ± 1.7	9.1 ± 1.9*	8.5 ± 1.5*	9.0 ± 1.5*	8.8 ± 1.4*	8.7 ± 1.4*
Hb_L [mg/dL]	11.0 ± 1.8	9.3 ± 2.0*	8.8 ± 1.8*	8.8 ± 1.9*	8.4 ± 2.0*	8.2 ± 1.8
Hb_E [mg/dL]	10.2 ± 1.6	9.0 ± 1.8	8.3 ± 1.3*	9.2 ± 1.2	9.0 ± 1.1*	9.0 ± 1.0*

of surgery cannot clearly be stated. However, incurring an increased risk of significant pulmonary fluid overload or critical reduction in pulmonary function seems not to be a clinically relevant problem.

In thoracic surgery, esophagectomy and lung surgery are counted amongst the most commonly performed surgical operations. In esophagectomy patients, clinical trials have demonstrated an increase in EVLWI [29, 30]. Oshima and colleagues reported values of EVLWI > 10 mL/kg perioperatively after esophagectomy without having a standardized protocol for fluid administration. Severe surgical trauma, lymphatic node extirpation, and systemic inflammatory response are seen as the main causes for this increase in EVLWI. Furthermore, OLV might also contribute to the development of a postoperative pulmonary edema, since it is known that OLV is correlated with pulmonary oxidative stress [21, 22]. In our study using SVV for guidance of fluid therapy, no significant increase of EVLWI in the subgroup of esophagectomy was found perioperatively and levels of EVLWI remained below 10 mL/kg.

In the patients that underwent lung surgery, EVLWI was even lower and did not exceed values of 9 mL/kg. However, the validity of EVLWI in lung surgery must be interpreted with caution, particularly if lung tissue is resected, as was the case in our study where pulmonary lobectomy and bilobectomy were performed. Basically, EVLWI is underestimated when lung tissue is resected because any decrease in pulmonary blood volume induced by lung tissue resection influences the intrathoracic blood volume. Since EVLWI is calculated as the difference between intrathoracic thermal volume and intrathoracic blood volume—which in this instance would be overestimated—EVLWI is underestimated following lung tissue resection [31, 32]. Therefore, the results of EVLWI in the lung surgery group might be regarded as artificially low. Even if EVLWI was underestimated by 20%, EVLWI would not exceed the maximum of 11 mL/kg as seen in the lung surgery group (the highest value of measurement at OLVTERM15) and not 9 mL/kg 24 hours after surgery. This level is still within a clinically acceptable range when related to the results of Sakka and coworkers who described an EVLWI > 12 mL/kg to be correlated with a worse outcome in critically ill patients [13].

Volume deficiency indicated by SVV was corrected using colloid infusion in our study. Crystalloid was administered only at a maintenance rate. Since it is known that, compared to colloids, only one fifth of the intravenously infused volume of crystalloids remains within the intravascular space, it must be assumed that a strategy based on a protocol using crystalloids exclusively would potentially have led to a higher EVLWI value and potentially a more pronounced deterioration in pulmonary function [33].

Gas exchange was reduced in the lung surgery group and in the esophagectomy group. In lung surgery, a decrease in the p_aO_2/F_iO_2-ratio can be explained by resection of lung tissue leading to a reduction of the alveolar surface necessary for gas exchange. In patients undergoing esophagectomy, postoperative deterioration of gas exchange (such as a decrease in the p_aO_2/F_iO_2-ratio) is common and clinically challenging [34–37]. However, the decrease in the p_aO_2/F_iO_2-ratio was only moderate and values always remained above 300 mmHg. Therefore, SVV-guided volume therapy seemed not to have aggravated this clinical problem.

After initiation of SVV-guided fluid management, CI was increased at two timepoints compared to the baseline measurement. Although the increase did not reach statistical significance at all timepoints, these data suggest that SVV-guided fluid management contributes to an improved CI even in open chest thoracic surgery, being the basis for optimization of tissue oxygenation.

GEDI did not change significantly during the observation period. This fact provides evidence that the volume replacement strategy oriented to SVV led to a stable preload condition in these patients. A comparison group with more restrictive fluid management would have been desirable at this point and certainly, the lack of this comparison group remains the major limitation of this study. Other limitations have to be taken into consideration. Only the total amount of fluid administration 24 hours after surgery was recorded, and

Table 4: Hemodynamic parameters and oxygenation. EVLWI: extravascular lung water index; CI: cardiac index; AP mean: mean arterial pressure; CVP: central venous pressure; GEDI: global enddiastolic volume index; SVI: stroke volume index; compliance: pulmonary compliance; NE: norepinephrine administration; *difference to BL in analysis of variance (ANOVA) ($P < 0.05$). BL: directly after induction of anesthesia; OLVimpl15: 15 minutes after beginning OLV; OLVterm15: 15 minutes after cessation of OLV; 6postop: 6 hours after surgery; 12postop: 12 hours after surgery; 24postop: 24 hours after surgery.

	BL	OLVimpl15	OLVterm15	6postop	12postop	24postop
$EVLWI_T$ [mL/kg]	7.8 ± 2.5	8.4 ± 3.9	8.5 ± 2.5	8.2 ± 2.9	8.7 ± 2.6	8.1 ± 2.4
$EVLWI_L$ [mL/kg]	7.9 ± 1.7	8.1 ± 3.2	8.5 ± 2.5	7.8 ± 2.4	8 ± 1.8	7.2 ± 1.9
$EVLWI_E$ [mL/kg]	7.8 ± 3	8.5 ± 3.4	8.6 ± 2.6	8.5 ± 3.1	8.98 ± 3	9.1 ± 2.5
p_aO_2/F_iO_2-$ratio_T$ [mmHg]	419 ± 122	186 ± 94*	334 ± 92*	n.d.	n.d.	n.d.
p_aO_2/F_iO_2-$ratio_L$ [mmHg]	462 ± 140	202 ± 105*	338 ± 112*	n.d.	n.d.	n.d.
p_aO_2/F_iO_2-$ratio_E$ [mmHg]	389 ± 101	174 ± 87*	332 ± 80	330 ± 111	329 ± 105	303 ± 74*
CI_T [L/min/m^2]	2.8 ± 0.9	3.6 ± 0.9*	3.5 ± 0.8	3.5 ± 0.9*	3.6 ± 0.9	3.5 ± 0.9
CI_L [L/min/m^2]	3 ± 0.9	3.4 ± 0.66	3.5 ± 0.8	3.6 ± 1.1	3.9 ± 1.2	3.6 ± 1.2
CI_E [L/min/m^2]	2.7 ± 0.9	3.7 ± 1*	3.5 ± 0.7	3.5 ± 0.6	3.5 ± 0.7	3.4 ± 0.6
AP $mean_T$ [mmHg]	78.7 ± 15	74.9 ± 14.1	73 ± 12.1	78.9 ± 14.1	73.9 ± 16.1	76.6 ± 8.2
AP $mean_L$ [mmHg]	84.8 ± 13.3	84.7 ± 12.6	80.1 ± 14.1	85.9 ± 11.7	81.3 ± 14.2	81.4 ± 6.9
AP $mean_E$ [mmHg]	74.5 ± 15	68.2 ± 11	68.1 ± 7.8	74 ± 13.7	69.5 ± 15.9	73.8 ± 7.7
CVP_T [mmHg]	7.4 ± 2	7.3 ± 2.9	6.6 ± 2.7	6.1 ± 2	5.8 ± 2.4	6 ± 2.2
CVP_L [mmHg]	7.9 ± 0.3	7.2 ± 2.5	6.4 ± 2.3	5.9 ± 2.2	5.4 ± 1.2	5.5 ± 1.5
CVP_E [mmHg]	7 ± 2.6	7.4 ± 3.3	6.8 ± 3	6.3 ± 1.9	6 ± 2.9	6.2 ± 2.6
$GEDI_T$ [mL/m^2]	673 ± 169	642 ± 152	633 ± 144	649 ± 114	665 ± 124	658 ± 123
$GEDI_L$ [mL/m^2]	702 ± 167	694 ± 121	689 ± 170	670 ± 93	657 ± 138	640 ± 101
$GEDI_E$ [mL/m^2]	653 ± 173	607 ± 165	594 ± 112	635 ± 128	670 ± 119	669 ± 137
SVI_T [mL/m^2]	40.2 ± 11.1	48.4 ± 12.4	46.9 ± 15.3	49.6 ± 13.6	49.7 ± 13.8	47.3 ± 13.9
SVI_E [mL/m^2]	38.9 ± 10.0	50.2 ± 13.7	46.7 ± 16.1	47.8 ± 12.3	47.1 ± 12.5	46.5 ± 12.8
SVI_L [mL/m^2]	42.0 ± 12.7	46.1 ± 10.4	47.1 ± 14.9	52.0 ± 15.5	53.1 ± 15.3	48.5 ± 15.8
$Compliance_T$ [L/cmH_2O]	0.049 ± 0.013	0.023 ± 0.006*	0.046 ± 0.012	n.d.	n.d.	n.d.
$Compliance_L$ [L/cmH_2O]	0.055 ± 0.014	0.024 ± 0.006*	0.045 ± 0.013	n.d.	n.d.	n.d.
$Compliance_E$ [L/cmH_2O]	0.046 ± 0.01	0.022 ± 0.005*	0.046 ± 0.012	0.039 ± 0.013	0.052 ± 0.023	0.062 ± 0.024
NE_T [μg/kg/min]	0.07 ± 0.02	0.12 ± 0.02	0.08 ± 0.01	0.04 ± 0.02	0.03 ± 0.01	0.02* ± 0.01
NE_L [μg/kg/min]	0.05 ± 0.01	0.09 ± 0.02	0.06 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.008* ± 0.01
NE_E [μg/kg/min]	0.08 ± 0.01	0.14 ± 0.01	0.09 ± 0.01	0.06 ± 0.02	0.04 ± 0.01	0.03* ± 0.01

thus fluid administration cannot be differentiated according to the time line BL-24postop. The validity of SVV and the validity of transpulmonary thermodilution parameters during OLV have not been explored in detail. Thus far only one clinical study has shown SVV to be a predictor for volume responsiveness during OLV [38]. Furthermore, after thoracotomy with open chest conditions, SVV is not without controversy regarding prediction of volume responsiveness [23–28]. However, our data has revealed that even if SVV-guided fluid management is not definitively validated under open chest conditions and OLV, severe pulmonary fluid overload is not inevitable.

Our study was not designed to demonstrate the clinical advantage of a SVV-guided fluid management in comparison to a control group. Furthermore, it is difficult to comment on any real safety in a study with a limited number of participants included, particularly when there is no comparison group. Therefore, our results have to be interpreted with caution. Nevertheless, our study forms the basis for further investigation regarding SVV-guided fluid management in thoracic surgery requiring open chest conditions and OLV, which has previously been effectively performed in other fields of surgery.

Conflict of Interests

Alwin E. Goetz and Daniel A. Reuter are members of the Medical Advisory Board of Pulsion Medical Systems. Apart from the conflict of interests mentioned above, all authors disclose (1) all funding sources, (2) any commercial or non-commercial affiliations, and (3) any other associations, such as consultancies.

References

[1] M. A. Hamilton, M. Cecconi, and A. Rhodes, "A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients," *Anesthesia and Analgesia*, vol. 112, no. 6, pp. 1392–1402, 2011.

[2] M. Buettner, W. Schummer, E. Huettemann, S. Schenke, N. Van Hout, and S. G. Sakka, "Influence of systolic-pressure-variation-guided intraoperative fluid management on organ function and oxygen transport," *British Journal of Anaesthesia*, vol. 101, no. 2, pp. 194–199, 2008.

[3] M. S. G. Goepfert, D. A. Reuter, D. Akyol, P. Lamm, E. Kilger, and A. E. Goetz, "Goal-directed fluid management reduces vasopressor and catecholamine use in cardiac surgery patients," *Intensive Care Medicine*, vol. 33, no. 1, pp. 96–103, 2007.

[4] J. Benes, I. Chytra, P. Altmann et al., "Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of prospective randomized study," *Critical Care*, vol. 14, no. 3, article R118, 2010.

[5] M. R. Lopes, M. A. Oliveira, V. O. S. Pereira, I. P. B. Lemos, J. O. C. Auler Jr., and F. Michard, "Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial," *Critical Care*, vol. 11, article R100, 2007.

[6] M. Licker, M. de Perrot, A. Spiliopoulos et al., "Risk factors for acute lung injury after thoracic surgery for lung cancer," *Anesthesia and Analgesia*, vol. 97, no. 6, pp. 1558–1565, 2003.

[7] N. W. Brister, R. E. Barnette, V. Kim, and M. Keresztury, "Anesthetic considerations in candidates for lung volume reduction surgery," *Proceedings of the American Thoracic Society*, vol. 5, no. 4, pp. 432–437, 2008.

[8] M. Sentürk, "New concepts of the management of one-lung ventilation," *Current Opinion in Anesthesiology*, vol. 19, pp. 1–4, 2006.

[9] K. D. Eichenbaum and S. M. Neustein, "Acute lung injury after thoracic surgery," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 24, no. 4, pp. 681–690, 2010.

[10] J. Lemson, L. E. van Die, A. E. A. Hemelaar, and J. G. van der Hoeven, "Extravascular lung water index measurement in critically ill children does not correlate with a chest x-ray score of pulmonary edema," *Critical Care*, vol. 14, no. 3, article R105, 2010.

[11] A. Laggner, G. Kleinberger, J. Haller, K. Lenz, G. Sommer, and W. Druml, "Bedside estimation of extravascular lung water in critically ill patients: comparison of the chest radiograph and the thermal dye technique," *Intensive Care Medicine*, vol. 10, no. 6, pp. 309–313, 1984.

[12] P. R. Eisenberg, A. S. Jaffe, and D. P. Schuster, "Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients," *Critical Care Medicine*, vol. 12, no. 7, pp. 549–553, 1984.

[13] S. G. Sakka, M. Klein, K. Reinhart, and A. Meier-Hellmann, "Prognostic value of extravascular lung water in critically ill patients," *Chest*, vol. 122, no. 6, pp. 2080–2086, 2002.

[14] E. R. Johnson and M. A. Matthay, "Acute lung injury: epidemiology, pathogenesis, and treatment," *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, vol. 23, no. 4, pp. 243–252, 2010.

[15] V. V. Kuzkov, M. Y. Kirov, M. A. Sovershaev et al., "Extravascular lung water determined with single transpulmonary thermodilution correlates with the severity of sepsis-induced acute lung injury," *Critical Care Medicine*, vol. 34, no. 6, pp. 1647–1653, 2006.

[16] G. S. Martin, S. Eaton, M. Mealer, and M. Moss, "Extravascular lung water in patients with severe sepsis: a prospective cohort study," *Critical Care*, vol. 9, no. 2, pp. R74–R82, 2005.

[17] J. Lohser, "Evidence-based Management of one-lung ventilation," *Anesthesiology Clinics*, vol. 26, no. 2, pp. 241–272, 2008.

[18] S. Haas, R. Kiefmann, V. Eichhorn, A. E. Goetz, and D. A. Reuter, "Hemodynamic monitoring in one-lung ventilation," *Anaesthesist*, vol. 58, no. 11, pp. 1085–1096, 2009.

[19] K. F. Cheong, "Re-expansion pulmonary oedema following one-lung ventilation—a case report," *Annals of the Academy of Medicine Singapore*, vol. 28, no. 4, pp. 572–573, 1999.

[20] Y. Asao, M. Kobayashi, N. Tsubaki, O. Kobayashi, and K. Uehara, "A case of re-expansion pulmonary edema after one lung ventilation for the radical operation of lung cancer," *The Japanese Journal of Anesthesiology*, vol. 52, no. 2, pp. 154–157, 2003.

[21] Y. J. Cheng, K. C. Chan, C. T. Chien, W. Z. Sun, and C. J. Lin, "Oxidative stress during 1-lung ventilation," *Journal of Thoracic and Cardiovascular Surgery*, vol. 132, no. 3, pp. 513–518, 2006.

[22] Y. Sugasawa, K. Yamaguchi, S. Kumakura et al., "The effect of one-lung ventilation upon pulmonary inflammatory responses during lung resection," *Journal of Anesthesia*, vol. 25, no. 2, pp. 170–177, 2011.

[23] D. A. Reuter, M. S. G. Goepfert, T. Goresch, M. Schmoeckel, E. Kilger, and A. E. Goetz, "Assessing fluid responsiveness during open chest conditions," *British Journal of Anaesthesia*, vol. 94, no. 3, pp. 318–323, 2005.

[24] D. A. Reuter, T. Goresch, M. S. G. Goepfert, S. M. Wildhirt, E. Kilger, and A. E. Goetz, "Effects of mid-line thoracotomy on the interaction between mechanical ventilation and cardiac filling during cardiac surgery," *British Journal of Anaesthesia*, vol. 92, no. 6, pp. 808–813, 2004.

[25] E. Lorne, Y. Mahjoub, E. Zogheib et al., "Influence of open chest conditions on pulse pressure variations," *Annales Francaises d'Anesthesie et de Reanimation*, vol. 30, no. 2, pp. 117–121, 2011.

[26] E. E. C. de Waal, S. Rex, C. L. J. J. Kruitwagen, C. J. Kalkman, and W. F. Buhre, "Dynamic preload indicators fail to predict fluid responsiveness in open-chest conditions," *Critical Care Medicine*, vol. 37, no. 2, pp. 510–515, 2009.

[27] P. A. H. Wyffels, P. Sergeant, and P. F. Wouters, "The value of pulse pressure and stroke volume variation as predictors of fluid responsiveness during open chest surgery," *Anaesthesia*, vol. 65, no. 7, pp. 704–709, 2010.

[28] M. Sander, C. D. Spies, K. Berger et al., "Prediction of volume response under open-chest conditions during coronary artery bypass surgery," *Critical Care*, vol. 11, no. 6, article R121, 2007.

[29] Y. Sato, S. Motoyama, K. Maruyama et al., "Extravascular lung water measured using single transpulmonary thermodilution reflects perioperative pulmonary edema induced by esophagectomy," *European Surgical Research*, vol. 39, no. 1, pp. 7–13, 2007.

[30] K. Oshima, F. Kunimoto, H. Hinohara et al., "Evaluation of respiratory status in patients after thoracic esophagectomy using PiCCO system," *Annals of Thoracic and Cardiovascular Surgery*, vol. 14, no. 5, pp. 283–288, 2008.

[31] R. Katzenelson, A. Perel, H. Berkenstadt et al., "Accuracy of transpulmonary thermodilution versus gravimetric measurement of extravascular lung water," *Critical Care Medicine*, vol. 32, no. 7, pp. 1550–1554, 2004.

[32] F. Michard, "Bedside assessment of extravascular lung water by dilution methods: temptations and pitfalls," *Critical Care Medicine*, vol. 35, no. 4, pp. 1186–1192, 2007.

[33] M. S. Strunden, K. Heckel, A. E. Goetz, and D. A. Reuter, "Perioperative fluid and volume management: physiological basis, tools and strategies," *Annals of Intensive Care*, vol. 1, article 2, 2011.

[34] P. L. Byth and A. J. Mullens, "Peri-operative care for oesophagectomy patients," *Australian Clinical Review*, vol. 11, no. 1-2, pp. 45–50, 1991.

[35] T. A. Crozier, M. Sydow, J. R. Siewert, and U. Braun, "Postoperative pulmonary complication rate and long-term changes in respiratory function following esophagectomy with esophagogastrostomy," *Acta Anaesthesiologica Scandinavica*, vol. 36, no. 1, pp. 10–15, 1992.

[36] B. Z. Atkins and T. A. D'Amico, "Respiratory complications after esophagectomy," *Thoracic Surgery Clinics*, vol. 16, no. 1, pp. 35–48, 2006.

[37] M. Ikeguchi, M. Maeta, and N. Kaibara, "Respiratory function after esophagecotomy for patients with esophageal cancer," *Hepato-Gastroenterology*, vol. 49, no. 47, pp. 1284–1286, 2002.

[38] K. Suehiro and R. Okutani, "Stroke volume variation as a predictor of fluid responsiveness in patients undergoing one-lung ventilation," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 24, no. 5, pp. 772–775, 2010.

Hindawi Publishing Corporation
Critical Care Research and Practice
Volume 2012, Article ID 821218, 10 pages
doi:10.1155/2012/821218

Clinical Study

Comparison of Goal-Directed Hemodynamic Optimization Using Pulmonary Artery Catheter and Transpulmonary Thermodilution in Combined Valve Repair: A Randomized Clinical Trial

Andrey I. Lenkin,[1,2] Mikhail Y. Kirov,[1,2,3,4] Vsevolod V. Kuzkov,[1,2] Konstantin V. Paromov,[1] Alexey A. Smetkin,[1,2] Mons Lie,[5] and Lars J. Bjertnæs[3,4]

[1] *Cardiosurgical Intensive Care Unit, City Hospital No. 1, Suvorov Street 1, Arkhangelsk 163001, Russia*
[2] *Department of Anesthesiology and Intensive Care Medicine, Northern State Medical University, Troitsky Avenue 51, Arkhangelsk 163000, Russia*
[3] *Department of Anesthesiology, University Hospital of North Norway, Tromsø, Norway*
[4] *Department of Clinical Medicine (Anesthesiology), Faculty of Medicine, University of Tromsø, 9037 Tromsø, Norway*
[5] *Office for International Cooperation, Oslo University Hospital, Kirkeveien 166, 0407 Oslo, Norway*

Correspondence should be addressed to Andrey I. Lenkin, www.starfish@mail.ru

Received 6 February 2012; Accepted 14 February 2012

Academic Editor: Samir Sakka

Our aim was to compare the effects of goal-directed therapy guided either by pulmonary artery catheter (PAC) or by transpulmonary thermodilution (TTD) combined with monitoring of oxygen transport on perioperative hemodynamics and outcome after complex elective valve surgery. *Measurements and Main Results*. Forty patients were randomized into two equal groups: a PAC group and a TTD group. In the PAC group, therapy was guided by mean arterial pressure (MAP), cardiac index (CI) and pulmonary artery occlusion pressure (PAOP), whereas in the TTD group we additionally used global end-diastolic volume index (GEDVI), extravascular lung water index (EVLWI), and oxygen delivery index (DO_2I). We observed a gradual increase in GEDVI, whereas EVLWI and PAOP decreased by 20–30% postoperatively ($P < 0.05$). The TTD group received 20% more fluid accompanied by increased stroke volume index and DO_2I by 15–20% compared to the PAC group ($P < 0.05$). Duration of mechanical ventilation was increased by 5.2 hrs in the PAC group ($P = 0.04$). *Conclusions*. As compared to the PAC-guided algorithm, goal-directed therapy based on transpulmonary thermodilution and oxygen transport increases the volume of fluid therapy, improves hemodynamics and DO_2I, and reduces the duration of respiratory support after complex valve surgery.

1. Introduction

Valve repair and replacement is a rapidly progressing and challenging type of cardiac surgery [1–3]. The outcome of valve surgery is influenced by a variety of factors including age and the general condition of the patient, preoperative severity of heart dysfunction, myocardial ischemia, and duration of cardiopulmonary bypass (CPB) [4, 5]. The latter may induce systemic inflammatory response syndrome (SIRS) and lead to multiorgan dysfunction syndrome (MODS) [6–10].

Several therapeutic approaches have been used to alleviate CPB-induced SIRS and MODS including goal-directed hemodynamic optimization [11]. Thus, complex monitoring could increase the efficacy of these therapies. Recently, so-called "less invasive" techniques for measurement of cardiac output (CO) have been implemented as a useful adjunct or even alternative to the hemodynamic monitoring by means of the pulmonary artery catheter (PAC). Among these various techniques, transpulmonary thermodilution, allowing measurement of volumetric parameters and subsequent continuous, "beat-to-beat" CO-computation based on pulse

contour analysis, has proved to be a valuable monitoring tool both in coronary surgery and heart failure [12–15]. However, its potential advantage in heart valve surgery in comparison with pressure-oriented hemodynamic monitoring, which is still widely used, has not been elucidated. This is especially interesting when taking into account that, before repair, valve diseases can distort the thermodilution curves, and thus, the results of the measurements.

Severe SIRS and MODS triggered by major cardiosurgical intervention and/or CPB can also disturb the oxygen transport. Hence, continuous measurement of either central venous ($ScvO_2$) or mixed venous (SvO_2) oxygen saturation may be a valuable adjunct to routine hemodynamic monitoring, which allows the determination of oxygen delivery and improves the outcome of several categories of critically ill patients [16, 17]. Recently introduced in clinical practice, the combination of continuous monitoring of CO and oxygen transport seems to be an attractive tool for displaying a "global hemodynamic view" and subsequent goal-directed perioperative optimization [18]. These algorithms have demonstrated their feasibility in both on-pump [19] and off-pump [15] coronary artery bypass grafting, but require further investigation in valve repair and replacement.

Therefore, the aim of this study was to evaluate the effect of treatment algorithms guided either by PAC or by transpulmonary thermodilution combined with monitoring of oxygen transport on perioperative hemodynamic management and outcome after complex valve surgery.

2. Materials and Methods

The study was approved by the Ethics Committee of Northern State Medical University, Arkhangelsk, Russia, in full compliance with the ethical standards as proclaimed by the Helsinki Declaration. Written informed consent was obtained from all patients or legal surrogate.

Forty-three adult patients scheduled for elective replacement/repair of two and more valves were enrolled into the single-centre study performed in an 850-bed university hospital during the period from March 2008 to June 2010. All operations were performed by the same surgical team. The inclusion criteria were age >18 years, presence of moderate or severe valve regurgitation and/or stenosis, and scheduled repair and/or replacement of two or more cardiac valves requiring CPB. The patients were excluded from the study if they had stenosis of coronary arteries requiring simultaneous coronary bypass grafting, extreme obesity (body mass index >40 kg m^{-1}), or participation in other investigations. Before the procedure, all patients were examined according to a standard protocol; risk of surgery was evaluated using the EuroSCORE system [20].

2.1. Clinical Protocol. On the day of surgery, patients were randomized into two groups using unmarked, sealed envelopes. Three patients were excluded from the analysis (Figure 1): two due to protocol violation (inability to reach study goals postoperatively caused in one case by massive blood loss and in another case—by PAC malfunction) and one due to inadequate surgical correction diagnosed by intraoperative transesophageal echocardiography (TEE). The hemodynamic optimization in the PAC group ($n = 20$) was targeted using parameters provided by PAC including pulmonary arterial occlusion pressure (PAOP) and cardiac index (CI) (LifeScope monitor, Nihon Kohden, Japan) (Figure 2(a)) (In cases of a PAOP < 12 mm Hg, a 500 mL bolus of 6% hydroxyaethyl starch 130/0.42 (Venofundin, B | Braun) was infused over 30 minutes aiming at a PAOP within the range of 12–18 mm Hg. The bolus infusion could be repeated once. If PAOP exceeded 18 mm Hg, nitroglycerin and/or furosemide and/or dobutamine were used on clinical judgment. If MAP was <60 mm Hg, an epinephrine infusion was started at 0.05 μg kg^{-1} min^{-1} with the option to increase the dose in 0.05 μg kg^{-1} min^{-1} increments, if required. In case of hypertension (MAP > 100 mm Hg), nitroglycerin infusion was administered in the dose range of 0.5–3.0 μg kg^{-1} min^{-1}. A transfusion trigger was Hb < 8 g dL^{-1}. Heart failure and low cardiac output syndrome (CI < 2.0 L min^{-1} m^{-2}) required a dobutamine infusion starting at 3.0 μg kg^{-1} min^{-1}. Central venous oxygen saturation ($ScvO_2$) was maintained >60%). In the group of transpulmonary thermodilution, the TTD group ($n = 20$), hemodynamics was managed using transpulmonary thermodilution including CI, global end-diastolic volume index (GEDVI), extravascular lung water index (EVLWI), and oxygen delivery index (DO_2I) as measured with the $PiCCO_2$ monitor (Pulsion Medical Systems, Munich, Germany) (Figure 2(b)) (In cases where GEDVI < 680 mm^{-2} and EVLWI < 10 mL kg^{-1}, a 500 mL bolus of 6% hydroxyethyl starch 130/0.42 was infused over 30 minutes aiming at a GEDVI within the range of 680–850 mL m^{-2}. The bolus infusion could be repeated. If GEDVI exceeded 850 mL kg^{-1}, nitroglycerin and/or furosemide and/or dobutamine were given on clinical judgement. In case of pulmonary edema (EVLWI > 10 mL kg^{-1}), we used intravenous administration of furosemide at a dose of 20 mg. If MAP was < 60 mm Hg, epinephrine infusion was started at 0.05 μg kg min^{-1} with an optional increment in dosage of 0.05 μg kg^{-1} min^{-1}. In cases of hypertension (MAP > 100 mm Hg), nitroglycerin infusion was given at a dose of 0.5–3.0 μg kg^{-1} min^{-1}. A transfusion trigger was Hb < 8.0 g dL^{-1}. Heart failure and low cardiac output syndrome (CI < 2.0 L min^{-1} m^{-2}) were treated with a dobutamine infusion starting at 3.0 μg kg^{-1} min^{-1} aimed at maintaining DO_2I in the range of 400–600 mL min^{-1} m^{-2}. $ScvO_2$ was maintained >60%). Mean arterial pressure (MAP), heart rate (HR), and hemoglobin concentration (Hb) were included into both the PAC- and the TTD-driven protocols. In both groups, $ScvO_2$ was maintained >60%. The algorithms for perioperative goal-directed therapy are depicted in Figure 2.

2.2. Anesthesia, Surgery, and Postoperative Care. All patients received standard premedication with diazepam. After arrival to the operation theatre, a femoral artery was catheterized either with standard 18G catheter (Arteriofix, B | Braun, Germany) in the PAC-group or with a 5F thermodilution catheter (PV2015L20 PULSOCATH, Pulsion Medical Systems) in the TTD group. After induction of anesthesia in the PAC group, a central venous introducer (Intradyn 8F,

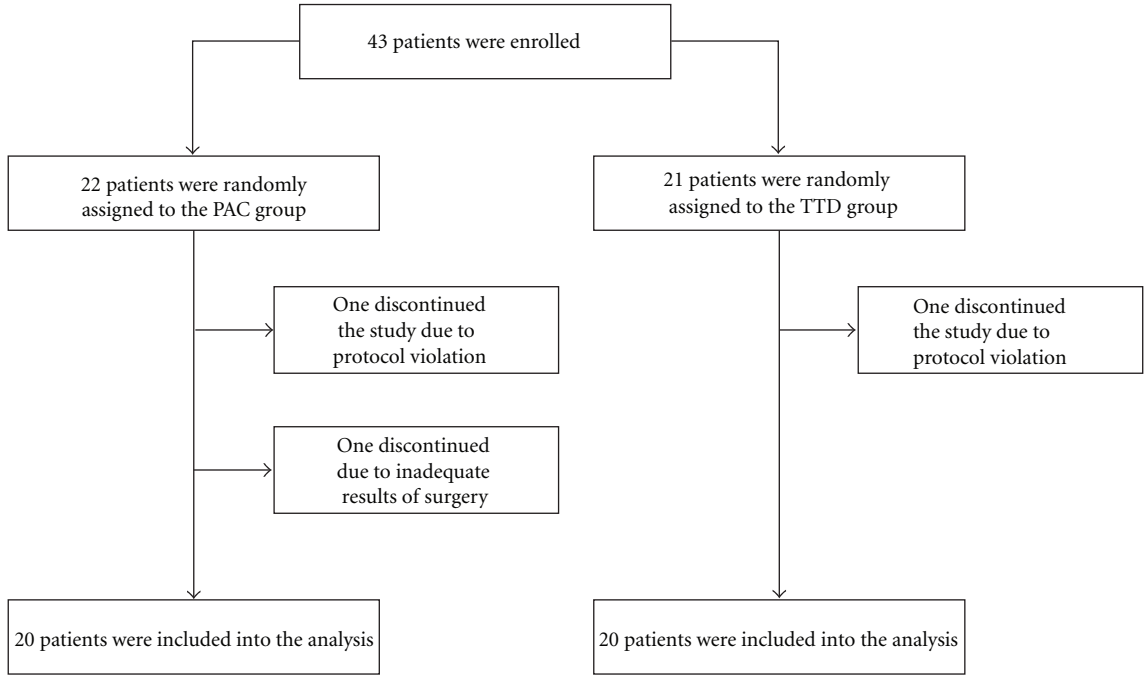


Figure 1: Flow diagram detailing the conduct of the study. PAC: pulmonary arterial catheter; TTD: transpulmonary thermodilution.

B | Braun) was inserted into the right internal jugular vein followed by a PAC (7.5F, Corodyn, B | Braun). The position of PAC and the adequacy of valve repair were verified by TEE (Acuson Cypress, Siemens, Germany) performed after CPB. In the TTD group, a triple-lumen central venous catheter (Certofix, B | Braun) and a fibre-optic probe (PV 2022–37, Pulsion Medical Systems) were inserted via the right jugular vein for continuous oxygen transport monitoring. Central venous pressure (CVP) was measured using either the venous port of the PAC or the middle port of the triple-lumen catheter in the PAC and the TTD groups, respectively.

Induction of anesthesia was performed with midazolam 0.07 mg kg^{-1}, propofol 1.0 mg kg^{-1} and fentanyl 5–7 $\mu g\,kg^{-1}$ in both groups. Anesthesia was maintained by continuous infusion of propofol (3–5 mg $kg^{-1}\,hr^{-1}$) and fentanyl (4-5 $\mu g\,kg^{-1}\,hr^{-1}$). Muscular paralysis for tracheal intubation was achieved by pipecuronium bromide 0.1 mg kg^{-1} and maintained with repeated doses of pipecuronium 0.015 mg $kg^{-1}\,hr^{-1}$ during operation. After intubation, volume-controlled mechanical ventilation (Fabius GS, Dräger, Germany) was provided with FiO_2 0.5, tidal volume 7-8 mL kg^{-1}, positive end-expiratory pressure (PEEP) 5 cm H_2O, and respiratory rate of 12–14 min^{-1}. For postoperative mechanical ventilation, we used Evita 4 (Dräger, Germany), maintaining a tidal volume of 7-8 mL kg^{-1} and a PEEP of 5 cm H_2O.

Cardiopulmonary bypass was performed in nonpulsatile mode with perfusion index of 3.0 L $min^{-1}\,m^{-2}$ using a standard roller-pump CPB-machine (Jostra HL 20, Maquet, Sweden). The priming of the reservoir was similar in both groups: 1000 mL Ringer's solution and 500 mL Gelofusine (B | Braun). For cardiac arrest and myocardial protection, we infused ice-cold (4–6°C) cardioplegic solution (Custodiol, Dr. F. Koehler Chemie GmbH, Germany) antegradely at an initial dose of 20 mL/kg. Restoration of cardiac function was either spontaneous or facilitated by means of an epicardial pacemaker. Weaning from CPB was performed in a stepwise manner. In case of heart failure diagnosed as CI below 2.0 L $min^{-1}\,m^{-2}$, we used dobutamine and/or epinephrine. Fluid replacement included crystalloid solutions (Sterofundin Iso/G5, B | Braun) with an initial infusion rate 6-7 mL $kg^{-1}\,hr^{-1}$ prior to and during anesthesia and 2-3 mL $kg^{-1}\,hr^{-1}$ postoperatively.

2.3. Measurements. In both groups, hemodynamic parameters as well as arterial and central venous blood gases, arterial hemoglobin, and lactate and glucose concentrations using ABL800Flex (Radiometer, Denmark) were evaluated after induction of anesthesia, at the end of surgery, and at 2, 6, 12, 18, and 24 hrs postoperatively. These perioperative stages were selected for goal-directed hemodynamic adjustments. In addition, plasma samples were taken before surgery and at 24 hrs postoperatively for the determination of probrain natriuretic peptide (NT-proBNP).

During the study, we evaluated perioperative fluid therapy, fluid balance, and inotrope/vasoactive support. The severity of postoperative MODS was estimated using the SOFA score [21]. For assessment of clinical outcome, we used duration of postoperative mechanical ventilation as the primary end-point and the length of ICU and hospital stay, and the mortality rate at Day 28 as the secondary end-points. The clinician responsible for the weaning from ventilation, ICU stay, and patient discharge was not involved in the study.

Criteria for termination of postoperative respiratory support were the following: a cooperative patient; adequate muscular tone; SpO_2 > 95% with FiO_2 0.5; $PaCO_2$ <45 mm Hg;

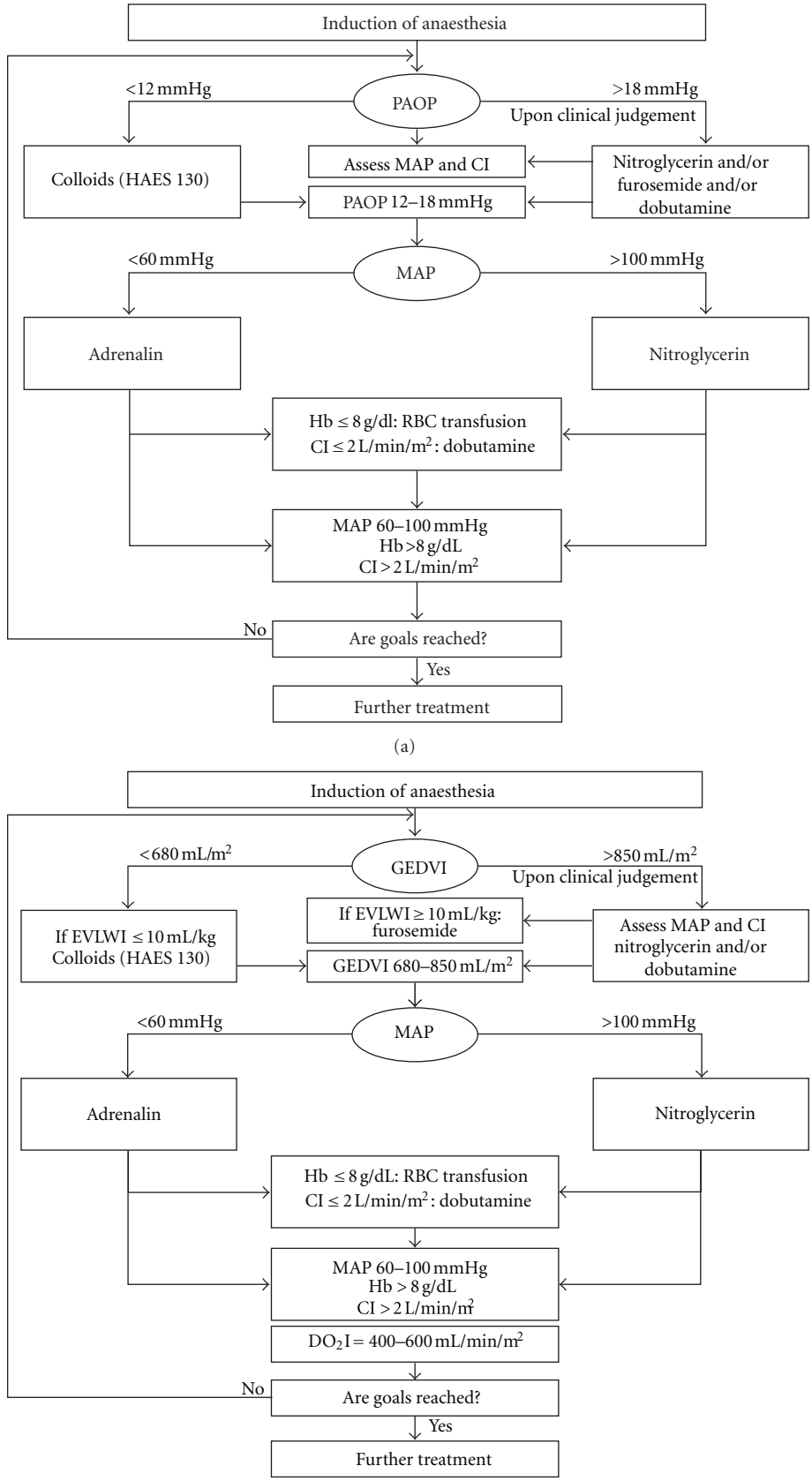


Figure 2: The algorithms of goal-directed hemodynamic optimization: (a) the PAC group, (b) the transpulmonary thermodilution (TTD) group. CPB: cardiopulmonary bypass; MAP: mean arterial pressure; PAOP: pulmonary artery occlusion pressure; CI: cardiac index; GEDVI: global end-diastolic volume index; EVLWI: extravascular lung water index; $ScvO_2$: central venous oxygen saturation; DO_2I: oxygen delivery index; Hb: hemoglobin concentration; RBC: red blood cells; HAES: hydroxyaethyl starch.

Table 1: Pre- and intraoperative characteristics of the study groups.

Parameter	TTD group	PAC group	P value
Age, yrs	54 ± 12	54 ± 10	0.97
EuroSCORE, points	7 ± 3	7 ± 3	0.81
EuroSCORE, predicted mortality risk, %	7.5 (5.0–13.8)	10.5 (4.0–14.8)	0.65
NYHA, functional class of heart failure	3 ± 0	3 ± 1	0.19
Left ventricular ejection fraction before surgery, %	57 ± 11	57 ± 10	0.90
Duration of surgery, min	234 ± 47	229 ± 41	0.72
Duration of aortic cross-clamping, min	105 ± 31	109 ± 31	0.69
Duration of cardiopulmonary bypass, min	142 ± 43	142 ± 37	0.97

TTD: transpulmonary thermodilution; PAC: pulmonary artery catheter. Data are presented as mean ± SD or median (25th–75th percentiles).

postoperative bleeding rate <50 mL hr^{-1}; stable hemodynamics without inotrope/vasopressor support; body temperature of >35°C. Temporary pacing was not regarded as a contraindication for tracheal extubation.

Length of ICU stay was registered when the patient's condition met the following "fit for discharge" criteria: fully oriented, SaO_2 > 90% on room air, no episodes of severe arrhythmias, bleeding <50 mL hr^{-1}, diuresis >0.5 mL kg^{-1} hr^{-1}, no need for inotrope/vasopressor support, and no signs of ischemia on ECG.

The patients were discharged from hospital when they satisfied the following criteria: hemodynamic stability, independence of ambulation and feeding, afebrile with no obvious infections, normal voiding and bowel movements, pain control on oral medications, and exercise tolerance.

2.4. Statistical Analysis. The SPSS 15.0 software package was used for statistical analysis. Calculation of sample size was based on initial observations (10 cases in each group) and the hypothesis that TTD will shorten the time of postoperative mechanical ventilation by 5 hrs compared with the PAC group. In order to find a statistically significant difference with α of 0.05 and power of 0.8, a sample size of 20 patients in each group proved to be sufficient. Data were checked for normal distribution by means of the Kolmogorov-Smirnov's test. Values are presented as mean ± standard deviation (SD) or median (25th–75th percentiles) for parametrically or nonparametrically distributed variables, respectively. In compliance with the distribution of data, Student's t-test or Mann-Whitney's U test were used for comparisons between groups. Intragroup comparisons were performed using test of contrasts. Discrete data were analyzed by two-sided χ^2-test or Fisher's exact test. For all tests, a P value < 0.05 was considered as significant.

3. Results

As shown in Table 1, we found no intergroup differences regarding demographic data, risk of surgery and severity of chronic illnesses, severity of heart failure, preoperative ejection fraction, durations of surgery, aortic cross-clamping, and CPB.

3.1. Hemodynamic Parameters. Table 2 demonstrates the changes in hemodynamics. In both groups, CVP rose at the end of surgery. Postoperatively, CVP declined transiently in the PAC group ($P < 0.05$) but returned to the baseline values by 24 hrs. In contrast, in the TTD group, CVP exceeded the corresponding values of the PAC group at 6 and 18 hrs ($P < 0.05$). In the TTD group, we observed a gradual postoperative increase in GEDVI and stroke volume variations (SVV) starting from 12 and 18 hrs, respectively, whereas EVLWI decreased by 20–30% ($P < 0.05$). In the PAC group, PAOP decreased significantly after operation.

By the end of intervention, MAP and SVRI were higher in the TTD group (Table 2; $P < 0.05$). Postoperatively, MAP and HR rose in both groups whereas SVRI decreased until 6 hrs compared with the preoperative values ($P < 0.05$). At 12 hrs, SVRI increased in the PAC group ($P = 0.03$), but decreased beyond 12 hrs postoperatively in the TTD group.

As shown in Figure 3, CI rose postoperatively by 55% in the TTD group and by 41% in the PAC group without intergroup difference. In parallel, SVI and DO_2I increased after the operation in both groups. However, from 6 hrs postoperatively SVI and DO_2I were higher by 15–20% in the TTD group ($P < 0.05$).

3.2. Oxygenation/Laboratory Parameters. Oxygenation and other laboratory data are shown in Table 3. Oxygenation ratio (PaO_2/FiO_2) did not differ significantly between the groups. At the end of surgery, PaO_2/FiO_2 decreased transiently in the TTD group, whereas $ScvO_2$ increased in comparison with the preoperative values in the PAC group ($P < 0.05$). At 12 hrs, $ScvO_2$ was higher in the PAC group ($P = 0.012$). After the intervention, pH decreased transiently in parallel with a rise in plasma lactate and a decline in Hb in both groups ($P < 0.05$) without intergroup differences. Base excess (BE) and $PaCO_2$ did not differ between the groups.

Postoperatively, we observed hyperglycemia, which was more pronounced in the PAC group but without significant intergroup difference (Table 3). The plasma concentrations of NT-proBNP rose postoperatively by 1045 pg mL^{-1} and 1315 pg mL^{-1} in the TTD and the PAC groups, respectively ($P > 0.05$). Preoperative serum creatinine concentrations were 0.08 ± 0.02 mmol L^{-1} and 0.09 ± 0.03 mmol L^{-1} in

Table 2: Changes in hemodynamic parameters in the study groups.

	Group	Before surgery	End of surgery	2 hrs	6 hrs	12 hrs	18 hrs	24 hrs
CVP, mm Hg	TTD group	12 ± 4	16 ± 4†	11 ± 4	12 ± 4*	11 ± 5	13 ± 5*	14 ± 4
	PAC group	13 ± 4	16 ± 3†	12 ± 4	10 ± 3†	10 ± 4†	11 ± 3†	12 ± 4
PAOP, mm Hg	PAC group	19 ± 7	18 ± 6	15 ± 6†	13 ± 4†	12 ± 5†	15 ± 6†	16 ± 3
GEDVI, mL m^{-2}	TTD group	757 ± 191	707 ± 63	719 ± 150	747 ± 106	815 ± 203†	824 ± 214†	839 ± 205†
SVV, %	TTD group	8 ± 5	13 ± 5	13 ± 6	13 ± 5	14 ± 7	15 ± 5†	16 ± 6†
EVLWI, mL kg^{-1}	TTD group	12 ± 4	11 ± 2†	10 ± 3†	9 ± 2†	10 ± 3	10 ± 3†	10 ± 2
MAP, mm Hg	TTD group	73 ± 15	72 ± 13*	74 ± 15	71 ± 8	80 ± 11	87 ± 16†	88 ± 15†
	PAC group	72 ± 17	66 ± 8	74 ± 11	71 ± 11	80 ± 11	87 ± 12†	82 ± 21
SVRI, $dyne \cdot sec^{-1}\, cm^{-5}\, m^{-2}$	TTD group	2732 ± 738	1913 ± 564*†	2093 ± 711†	1730 ± 443†	1948 ± 534*†	2216 ± 692†	2073 ± 517†
	PAC group	2610 ± 1039	1466 ± 411†	1962 ± 644†	2030 ± 618†	2345 ± 716	2493 ± 626	2286 ± 581
HR, min^{-1}	TTD group	65 ± 12	82 ± 22†	78 ± 11†	74 ±11†	75 ± 15†	77 ± 14†	74 ± 11†
	PAC group	71 ± 14	79 ± 12†	78 ± 11†	79 ± 14†	75 ± 15	77 ± 13	80 ± 13†

TTD: transpulmonary thermodilution; PAC: pulmonary artery catheter; CVP: central venous pressure; PAOP: pulmonary artery occlusion pressure; GEDVI: global end-diastolic volume index; EVLWI: extravascular lung water index; MAP: mean arterial pressure; SVRI: systemic vascular resistance index; HR: heart rate.
*$P < 0.05$ between the groups; †$P < 0.05$ within the group compared with the preoperative value. Data are presented as mean ± SD.

Table 3: Changes in oxygenation and laboratory parameters in the study groups.

Parameter	Group	Before surgery	End of surgery	2 hrs	6 hrs	12 hrs	18 hrs	24 hrs
PaO_2/FiO_2, mm Hg	TTD group	330 ± 104	269 ± 129†	322 ± 124	329 ± 102	337 ± 137	311 ± 114	291 ± 82
	PAC group	279 ± 114	234 ± 89	286 ± 96	325 ± 87	324 ± 76	309 ± 101	310 ± 134
$ScvO_2$, %	TTD group	73 ± 10	71 ± 15	69 ± 10	66 ± 14	69 ± 11*	65 ± 14†	66 ± 8†
	PAC group	70 ± 9	78 ± 10†	74 ± 10	75 ± 10	75 ± 14†	67 ± 14	65 ± 9
pH	TTD group	7.39 ± 0.04	7.34 ± 0.01†	7.35 ± 0.04†	7.34 ± 0.07†	7.35 ± 0.07†	7.38 ± 0.05	7.41 ± 0.05†
	PAC group	7.38 ± 0.05	7.34 ± 0.05†	7.33 ± 0.06†	7.38 ± 0.05	7.39 ± 0.05	7.42 ± 0.05†	7.43 ± 0.04†
Lactate, mmol L^{-1}	TTD group	0.9 ± 0.3	2.8 ± 1.0†	2.2 ± 1.1†	3.3 ± 2.1†	3.6 ± 2.2†	2.5 ± 1.6†	2.2 ± 1.1†
	PAC group	0.9 ± 0.3	3.0 ± 0.9†	2.5 ± 1.2†	3.5 ± 2.1†	4.0 ± 2.6†	2.5 ± 1.2†	2.1 ± 0.6†
Hb, g dL^{-1}	TTD group	12.7 ± 1.9	9.0 ± 1.4†	10.1 ± 2.1†	10.5 ± 1.7†	11.1 ± 1.3†	11.0 ± 1.5†	10.9 ± 1.3†
	PAC group	11.7 ± 1.4	8.4 ± 1.2†	9.6 ± 2.0†	10.5 ± 1.4†	10.7 ± 1.4†	10.6 ± 1.2†	10.6 ± 1.7†
Glucose, mmol L^{-1}	TTD group	5.8 ± 2.0	7.3 ± 3.2	7.6 ± 3.7	11.9 ± 4.1†	12.0 ± 6.9†	8.7 ± 2.2†	7.8 ± 3.1
	PAC group	5.8 ± 1.7	8.5 ± 4.3†	8.4 ± 3.4†	10.3 ± 3.9†	12.8 ± 4.7†	9.3 ± 3.7†	8.6 ± 5.5†

TTD: transpulmonary thermodilution; PAC: pulmonary artery catheter; PaO_2: partial arterial oxygen pressure; FiO_2: fraction of inspired oxygen; $ScvO_2$: central venous oxygen saturation; Hb: hemoglobin.
*$P < 0.05$ between the groups; †$P < 0.05$ within the group compared with the preoperative value. Data are presented as mean ± SD.

the TTD and the PAC groups, respectively. At 24 hrs after surgery, there was a trend towards increased creatinine values in the PAC group (0.148 ± 0.02 mmol L^{-1} versus 0.125 ± 0.03 mmol L^{-1}) in the TTD group ($P = 0.08$).

3.3. Clinical Characteristics and Outcomes. The clinical characteristics and outcomes are presented in Table 4.

Although the volume of crystalloids administered during surgery did not differ significantly between the groups, the TTD group received 24% more crystalloids and a threefold more colloids postoperatively ($P < 0.05$). The total volume of postoperative fluid therapy in this group exceeded that of the PAC group by 20% ($P = 0.01$). The incidence of colloid administration and the postoperative fluid balance tended to be higher in the TTD group; by contrast, the incidence and duration of inotropic/vasopressor support in this group demonstrated a trend towards lower doses as compared to the PAC-monitored patients. The incidence of diuretic administration, postoperative diuresis, blood loss and transfusion requirements, and the SOFA score at 24 hrs did not differ between the groups. The rate of pericardial pacing was similar: 70% and 60% in the PAC group and the TTD group, respectively.

The requirement for renal replacement therapy was also similar (one patient in each group). One patient in each group presented with a postoperative stroke. There was no wound infection in the studied patient population.

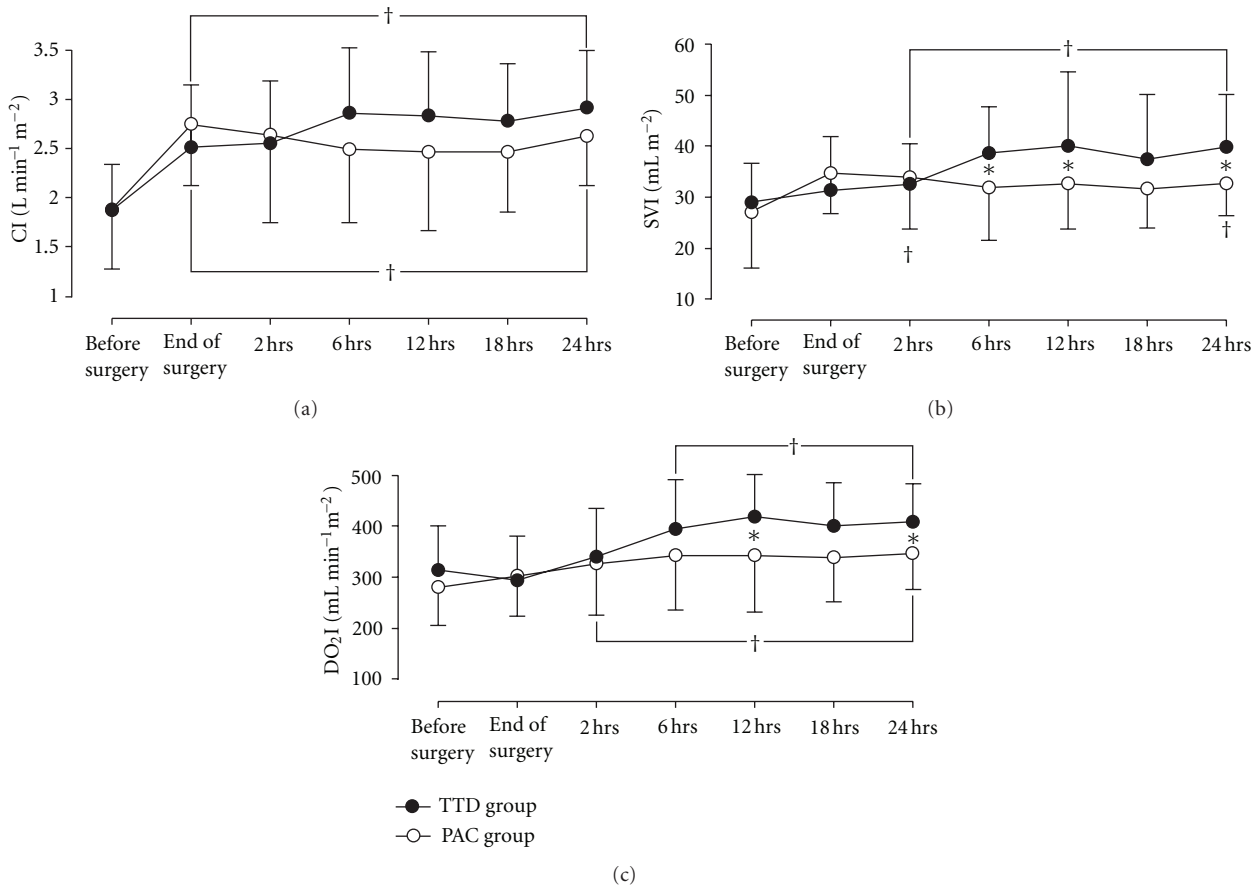


Figure 3: Changes in cardiac index, stroke volume index and oxygen delivery in the study groups. CI: cardiac index; SVI: stroke volume index; DO_2I: oxygen delivery index. $^*P < 0.05$ between the groups; $^\dagger P < 0.05$ within the group compared with the preoperative value. Data are presented as mean ± SD.

Duration of postoperative respiratory support increased by 36% in the PAC group (Table 4, $P = 0.04$). However, the duration of ICU stay and hospitalization did not differ. All the patients included in the study survived at Day 28.

4. Discussion

The study demonstrates that transpulmonary thermodilution combined with continuous monitoring of oxygen delivery may be used for detection of disorders in hemodynamics and oxygen transport that might influence the perioperative therapy after complex valve surgery.

Complex valve repair results in significant changes in preload. In this study, we found an increase in CVP after CPB in both groups, which is typical for these cardiac interventions [22]. In the TTD group, GEDVI rose after surgery in parallel with increased fluid therapy, whereas EVLWI declined. This finding can be explained by inclusion of colloids according to the treatment algorithm and by the rise in myocardial performance following valve repair. Postoperatively, the patients in the PAC group displayed decreases in the CVP and PAOP values. The reduction in these preload parameters may be caused by several mechanisms: by discontinuation of mechanical ventilation with PEEP and restoration of spontaneous breathing; for the second, from increased heart performance, and finally, from the relatively restrictive fluid regimen in the PAC group. The increase of SVV that we observed in patients of the TTD group at the end of the first postoperative day may be explained mainly by cessation of respiratory support. These results correspond with other studies of goal-directed therapy in cardiac surgery [12, 19, 23, 24].

At the end of surgery, we found lower MAP and SVRI values in the PAC group. Systemic vasodilatation can be explained by the CPB-induced SIRS that might be attenuated by the TTD-driven fluid therapy including colloids [11, 25]. In contrast to the TTD group, the patients of the PAC group presented with systemic vasoconstriction postoperatively, as evidenced by the increase in SVRI, which we interpret as a compensatory mechanism counteracting the reduced blood volume [26].

In addition to the changes in afterload, both groups had increased postoperative heart rate and myocardial contractility that is confirmed by an increase in CI and SVI. These changes can be caused by correction of the valvular malfunctions, restoration of myocardial function and hemodilution in parallel with fluid therapy [27]. Despite the transient perioperative changes in arterial and central venous oxygenation,

Table 4: Clinical characteristics of the study groups.

Characteristic	TTD group	PAC group	*P* value
Crystalloids intraoperatively, mL	1290 ± 213	1158 ± 327	0.14
Crystalloids during 24 hrs postoperatively, mL	1875 ± 531	1518 ± 410	**0.02**
Colloids during 24 hrs postoperatively, mL	250 ± 68	75 ± 41†	**0.04**
Incidence of colloid administration	15%	45%	0.08
Fluids during 24 hrs postoperatively, mL	1850 (1600–2575)	1550 (1312–1700)	**0.01**
Incidence of inotropic/vasopressor support	35%	65%	0.11
Duration of inotropic/vasopressor support after operation, hrs	11.9 ± 4.6	17.1 ± 3.8	0.14
Incidence of diuretic administration	30%	55%	0.20
Fluid balance at 24 hrs postoperatively, mL	85 (−358–940)	−743 (−1275–196)	0.05
Diuresis at 24 hrs postoperatively, mL	2410 ± 1196	2439 ± 959	0.93
Postoperative drainage blood loss, mL	557 ± 108	584 ± 190	0.21
SOFA score at 24 hrs postoperatively, points	5 ± 1	6 ± 1	0.37
Duration of respiratory support, hrs	14.3 ± 5.1	19.4 ± 5.8	**0.04**
Length of ICU stay, hrs	61.5 ± 37.2	64.1 ± 37.8	0.70
Length of hospital stay, days	20.7 ± 7.8	22.0 ± 7.8	0.60

TTD: transpulmonary thermodilution; PAC: pulmonary artery catheter. Data are presented as %, mean ± SD or median (25th–75th percentiles).

we observed an increase in oxygen delivery in parallel with regress of metabolic acidosis at 24 hrs postoperatively in both groups. These results confirm the efficacy of the goal-directed hemodynamic optimization. Therapy that increased oxygen transport attenuates the surgical stress and the hypoperfusion following combined CPB and valve repair [28]. In our investigation, this stress was manifested by hyperglycemia, a rise in NT-proBNP, and increase in plasma lactate in both groups. Similar findings have been described by other authors who assessed the effects of CPB and combined valve surgery [29, 30].

The preload optimization following valve repair in the TTD group might have contributed to an increase in heart performance with higher SVI compared with the PAC group. Similar results were obtained by Hofer et al. in a general ICU population [31] and by Brock et al. in patients undergoing cardiac surgery [32]. As a result of goal-directed therapy, the patients in the TTD group received more crystalloids and colloids and tended to receive less inotropic and vasopressor agents postoperatively. In cardiosurgical patients, similar results have been reported [19, 33]. Correction of hypovolaemia and cardiac output according to the study algorithm resulted in a better oxygen delivery and reduced the duration of respiratory support in the TTD group. These findings are consistent with beneficial effects of goal-directed therapy both in coronary and general surgery patients [15, 18, 19].

The observed intergroup differences might not result solely from the net volume of fluids but also from the accuracy of hemodynamic parameters used for preload assessment. Indeed, PAOP has been demonstrated to have a limitation as a preload marker [34]. In contrast, GEDVI is a more reliable marker of preload indicating the filling volume of all heart chambers, while PAOP barely reflects filling pressure of the left atrium [35].

Perioperative goal-directed therapy should be early, adequate, and individualized. Maintaining "supranormal" cardiac output and oxygen delivery does not improve the clinical outcome [36], thus we targeted to keep DO_2I values within the range of 400–600 mL min^{-1} m^{-2}. Although one of the aims of our treatment algorithms in both groups was to maintain CI > 2.0 L min^{-1} m^{-2}, we did not reach mean DO_2I values > 400 mL min m^{-2} in the PAC group. Interestingly, despite lower oxygen delivery, mean $ScvO_2$at 12 hrs was higher in the PAC group, which might indicate decreased oxygen consumption. Thus, although CI and $ScvO_2$ are important determinants of oxygen transport in high-risk patients, they should be accompanied by assessment of DO_2I for the most efficient guidance of postoperative care. Moreover, some conditions such as severe pulmonary hypertension might require simultaneous measurement of both volumetric parameters and pulmonary arterial pressures, using either PAC catheter or echocardiography for optimization of the hemodynamic management.

Better oxygen transport might influence organ function and improve clinical outcome. In our study, the PAC group tended to present with increased plasma creatinine concentrations postoperatively. This group received less fluid, which possibly contributed to hypoperfusion and impaired renal function [37]. Other investigators have demonstrated that perioperative goal-directed therapy may have a protective effect on organ function, reducing the number of complications and even decreasing mortality, especially in high-risk patients [16, 18, 38].

This study has several limitations related to the differences in study algorithms. Firstly, we did not measure PAOP in the TTD group or GEDVI in the PAC group. The reason was that the possibility for the attending physician to evaluate the volumetric parameters in the PAC group and the PAC-derived variables in the TTD group could have

influenced the choice of fluid therapy. Secondly, in the PAC group, in contrast to the TTD group, DO_2I was determined intermittently and was not included in the algorithm of goal-directed therapy. However, although the oxygen transport in the TTD group was monitored continuously, it required calibration with discrete measurement of blood gases at the same time points like in the PAC group. Moreover, this single-centre study has a limited number of observations and was not powered for demonstrating the reduction in ICU and hospital stay in the TTD group.

5. Conclusions

As compared to a PAC-guided treatment algorithm, goal-directed therapy based on transpulmonary thermodilution combined with monitoring of oxygen transport changes the strategy of fluid management, which in turn, improves hemodynamics and oxygen delivery and reduces the duration of postoperative respiratory support after complex valve surgery.

Acknowledgments

The authors thank the personnel of the operating theatre and the cardiosurgical ICU, City Hospital No. 1 of Arkhangelsk, for their kind assistance during the conduct of the investigation. M. Kirov is a member of the Medical Advisory Board of Pulsion Medical Systems.

References

[1] V. T. Nkomo, J. M. Gardin, T. N. Skelton, J. S. Gottdiener, C. G. Scott, and M. Enriquez-Sarano, "Burden of valvular heart diseases: a population-based study," *The Lancet*, vol. 368, no. 9540, pp. 1005–1011, 2006.

[2] S. Nathaniel, S. Saligram, and A. L. Innasimuthu, "Aortic stenosis: an update," *World Journal of Cardiology*, vol. 2, no. 6, pp. 135–139, 2010.

[3] E. Marijon, D. S. Celermajer, M. Tafflet et al., "Rheumatic heart disease screening by echocardiography: the inadequacy of world health organization criteria for optimizing the diagnosis of subclinical disease," *Circulation*, vol. 120, no. 8, pp. 663–668, 2009.

[4] R. Prêtre and M. I. Turina, "Cardiac valve surgery in the octogenarian," *Heart*, vol. 83, no. 1, pp. 116–121, 2000.

[5] J. Turina, T. Stark, B. Seifert, and M. Turina, "Predictors of the long-term outcome after combined aortic and mitral valve surgery," *Circulation*, vol. 100, no. 19, pp. II48–II53, 1999.

[6] S. C. Clark, "Lung injury after cardiopulmonary bypass," *Perfusion*, vol. 21, no. 4, pp. 225–228, 2006.

[7] Y. Abu-Omar and C. Ratnatunga, "Cardiopulmonary bypass and renal injury," *Perfusion*, vol. 21, no. 4, pp. 209–213, 2006.

[8] S. K. Ohri and T. Velissaris, "Gastrointestinal dysfunction following cardiac surgery," *Perfusion*, vol. 21, no. 4, pp. 215–223, 2006.

[9] D. J. Kennedy and J. F. Butterworth, "Endocrine function during and after cardiopulmonary bypass: recent observations," *Journal of Clinical Endocrinology and Metabolism*, vol. 78, no. 5, pp. 997–1002, 1994.

[10] J. Milot, J. Perron, Y. Lacasse, L. Létourneau, P. C. Cartier, and F. Maltais, "Incidence and predictors of ARDS after cardiac surgery," *Chest*, vol. 119, no. 3, pp. 884–888, 2001.

[11] S. Hirai, "Systemic inflammatory response syndrome after cardiac surgery under cardiopulmonary bypass," *Annals of Thoracic and Cardiovascular Surgery*, vol. 9, no. 6, pp. 365–370, 2003.

[12] M. Y. Kirov, A. I. Lenkin, V. V. Kuzkov et al., "Single transpulmonary thermodilution in off-pump coronary artery bypass grafting: hemodynamic changes and effects of different anesthetic techniques," *Acta Anaesthesiologica Scandinavica*, vol. 51, no. 4, pp. 426–433, 2007.

[13] S. Ritter, A. Rudiger, and M. Maggiorini, "Transpulmonary thermodilution-derived cardiac function index identifies cardiac dysfunction in acute heart failure and septic patients: an observational study," *Critical Care*, vol. 13, no. 4, p. R133, 2009.

[14] P. S. Halvorsen, A. Espinoza, R. Lundblad et al., "Agreement between PiCCO pulse-contour analysis, pulmonal artery thermodilution and transthoracic thermodilution during off-pump coronary artery by-pass surgery," *Acta Anaesthesiologica Scandinavica*, vol. 50, no. 9, pp. 1050–1057, 2006.

[15] A. A. Smetkin, M. Y. Kirov, V. V. Kuzkov et al., "Single transpulmonary thermodilution and continuous monitoring of central venous oxygen saturation during off-pump coronary surgery," *Acta Anaesthesiologica Scandinavica*, vol. 53, no. 4, pp. 505–514, 2009.

[16] R. Pearse, D. Dawson, J. Fawcett, A. Rhodes, R. M. Grounds, and E. D. Bennett, "Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial," *Critical care*, vol. 9, no. 6, pp. R687–R693, 2005.

[17] E. Rivers, B. Nguyen, S. Havstad et al., "Early goal-directed therapy in the treatment of severe sepsis and septic shock," *The New England Journal of Medicine*, vol. 345, no. 19, pp. 1368–1377, 2001.

[18] M. Y. Kirov, V. V. Kuzkov, and Z. Molnar, "Perioperative haemodynamic therapy," *Current Opinion in Critical Care*, vol. 16, no. 4, pp. 384–392, 2010.

[19] M. S. G. Goepfert, D. A. Reuter, D. Akyol, P. Lamm, E. Kilger, and A. E. Goetz, "Goal-directed fluid management reduces vasopressor and catecholamine use in cardiac surgery patients," *Intensive Care Medicine*, vol. 33, no. 1, pp. 96–103, 2007.

[20] J. Heikkinen, F. Biancari, J. Satta et al., "Predicting immediate and late outcome after surgery for mitral valve regurgitation with EuroSCORE," *The Journal of Heart Valve Disease*, vol. 16, no. 2, pp. 116–121, 2007.

[21] A. E. Jones, S. Trzeciak, and J. A. Kline, "The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation," *Critical Care Medicine*, vol. 37, no. 5, pp. 1649–1654, 2009.

[22] P. E. Marik, M. Baram, and B. Vahid, "Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares," *Chest*, vol. 134, no. 1, pp. 172–178, 2008.

[23] P. M. Kapoor, M. Kakani, U. Chowdhury, M. Choudhury, Lakshmy, and U. Kiran, "Early goal-directed therapy in moderate to high-risk cardiac surgery patients," *Annals of Cardiac Anaesthesia*, vol. 11, no. 1, pp. 27–34, 2008.

[24] A. M. Roche, T. E. Miller, and T. J. Gan, "Goal-directed fluid management with trans-oesophageal doppler," *Best Practice and Research*, vol. 23, no. 3, pp. 327–334, 2009.

[25] A. Mekontso-Dessap, R. Houël, C. Soustelle, M. Kirsch, D. Thébert, and D. Y. Loisance, "Risk factors for post-cardiopulmonary bypass vasoplegia in patients with preserved left

ventricular function," *Annals of Thoracic Surgery*, vol. 71, no. 5, pp. 1428–1432, 2001.

[26] R. G. Evans, S. Ventura, R. A. Dampney, and J. Ludbrook, "Neural mechanisms in the cardiovascular responses to acute central hypovolaemia," *Clinical and Experimental Pharmacology and Physiology*, vol. 28, no. 5-6, pp. 479–487, 2001.

[27] Y. Ohe, K. Satoh, N. Kobayashi, C. Tachibana, T. Fukada, and Y. Furuya, "Changes in respiration and hemodynamics during open heart surgery without blood transfusion," *Masui*, vol. 42, no. 8, pp. 1136–1141, 1993.

[28] S. Perz, T. Uhlig, M. Kohl et al., "Low and "supranormal" central venous oxygen saturation and markers of tissue hypoxia in cardiac surgery patients: a prospective observational study," *Intensive Care Medicine*, vol. 37, no. 1, pp. 52–59, 2010.

[29] M. Weber, M. Hausen, R. Arnold et al., "Prognostic value of N-terminal pro-B-type natriuretic peptide for conservatively and surgically treated patients with aortic valve stenosis," *Heart*, vol. 92, no. 11, pp. 1639–1644, 2006.

[30] S. B. Shinde, K. K. Golam, P. Kumar, and N. D. Patil, "Blood lactate levels during cardiopulmonary bypass for valvular heart surgery," *Annals of Cardiac Anaesthesia*, vol. 8, no. 1, pp. 39–44, 2005.

[31] C. K. Hofer, L. Furrer, S. Matter-Ensner et al., "Volumetric preload measurement by thermodilution: a comparison with transoesophageal echocardiography," *British Journal of Anaesthesia*, vol. 94, no. 6, pp. 748–755, 2005.

[32] H. Brock, C. Gabriel, D. Bibl, and S. Necek, "Monitoring intravascular volumes for postoperative volume therapy," *European Journal of Anaesthesiology*, vol. 19, no. 4, pp. 288–294, 2002.

[33] D. A. Reuter, T. W. Felbinger, K. Moerstedt et al., "Intrathoracic blood volume index measured by thermodilution for preload monitoring after cardiac surgery," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 16, no. 2, pp. 191–195, 2002.

[34] S. Uchino, R. Bellomo, H. Morimatsu et al., "Pulmonary artery catheter versus pulse contour analysis: a prospective epidemiological study," *Critical Care*, vol. 10, p. R174, 2006.

[35] C. Wiesenack, C. Prasser, C. Keyl, and G. Rödig, "Assessment of intrathoracic blood volume as an indicator of cardiac preload: single transpulmonary thermodilution technique versus assessment of pressure preload parameters derived from a pulmonary artery catheter," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 15, no. 5, pp. 584–588, 2001.

[36] M. Poeze, J. W. Greve, and G. Ramsay, "Meta-analysis of hemodynamic optimization: relationship to methodological quality," *Critical care*, vol. 9, no. 6, pp. R771–R779, 2005.

[37] J. W. Sear, "Kidney dysfunction in the postoperative period," *British Journal of Anaesthesia*, vol. 95, no. 1, pp. 20–32, 2005.

[38] M. T. Giglio, M. Marucci, M. Testini, and N. Brienza, "Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials," *British Journal of Anaesthesia*, vol. 103, no. 5, pp. 637–646, 2009.