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Influence of Tidal Volume on Pulse Pressure Variations in Hypovolemic Ventilated Pigs with Acute Respiratory Distress-like Syndrome

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ABSTRACT

Background: Sensitivity and specificity of respiratory change in pulse pressure (ΔPP) to predict preload dependency has been questioned at small tidal volumes (V_T) in critically ill patients suffering from acute respiratory distress syndrome (ARDS). We studied ΔPP in pigs with ARDS-like syndrome during reversible hemorrhagic shock.

Methods: Prospective, observational animal study in a Laboratory Investigation Unit. Sixteen deeply sedated mechanically ventilated pigs were successively ventilated with V_T of 10 ml/kg at a respiratory rate of 15 breaths/min (RR15) and V_T of 6 ml/kg at RR15 and RR25. ARDS-like syndrome was produced by lung lavage in eight pigs (ARDS group). Severe hemorrhagic shock was induced by removal of 40% of total blood volume followed by restoration.

Results: After bleeding, in the control group ventilated with a V_T of 10 ml/kg, ΔPP increased from 8.5 (95% confidence interval [CI], 7.1 to 9.9%) to 18.5% (CI, 15.3 to 21.7%; $P < 0.05$). In the ARDS group, this index increased similarly, from 7.1% (95% CI, 5.3 to 9.0%) to 20.1% (CI, 15.3 to 24.9%; $P < 0.05$). In control lungs, reduction in V_T from 10 to 6 ml/kg reduced the ΔPP reaction by 40%, although it remained a statistically valid indicator of hypovolemia regardless of the RR value. In contrast, in the ARDS group, ΔPP was an unreliable hypovolemia marker at low V_T ventilation, regardless of the RR value (p = not statistically significant).

Conclusions: The present study suggests that ΔPP is a reliable indicator of severe hypovolemia in pigs with healthy lungs regardless of V_T or RR. In contrast, in pigs with ARDS-like syndrome ventilated with small V_T, ΔPP is not a good indicator of severe hemorrhage. However, in this setting, indexing ΔPP to respiratory changes in transpulmonary pressure allows this marker to significantly indicate the occurrence of hypovolemia.

What We Already Know about This Topic

- Inappropriate fluid administration to patients with acute respiratory syndrome can result in pulmonary and interstitial edema.
- Dynamic measures of fluid responsiveness have been questioned at small tidal volumes in critically ill patients suffering from acute respiratory distress syndrome.

What This Article Tells Us That Is New

- In healthy pigs, respiratory change in pulse pressure is a good indicator of volume status, but it is not a good indicator in pigs with acute respiratory distress syndrome and ventilated with small tidal volumes.

INAPPROPRIATE fluid administration to intensive care patients can result in pulmonary and interstitial edema.[1,2] Traditional markers of fluid responsiveness based on static preload measurements (*i.e.*, cardiac pressures and volumes) are not reliable predictors of fluid responsiveness because individual Frank-Starling curves may vary among patients, resulting in a positive response to fluid challenge (preload dependency) or no response (preload independency).[3,4] In contrast to static preload indices, dynamic indices are good indicators of volume and usually predict fairly well individ-

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ual responses to volume loading.[5–9] Indeed, pulse pressure variation (ΔPP) was reported to accurately assess circulatory volume and predict fluid responsiveness in critically ill patients.[3,4] Other groups have used other indicators of stroke volume variations.[5,6,10–15] However, the majority of patients in these studies were ventilated with large tidal volumes (V_T greater than or equal to 8 ml/kg), and recent studies[16–19] have suggested that ΔPP is an unreliable indicator of fluid responsiveness at low V_T in patients suffering from the adult respiratory distress syndrome (ARDS). This is particularly important because patients with acute lung injury or ARDS should be ventilated with V_T less than 6 ml/kg.[20,21]

Patients with ARDS have reduced lung compliance (C_L) because of stiffer lung parenchyma, and some authors have demonstrated that this phenomenon dampens airway pressure transmission to the pleural space.[22] On the other hand, a decrease in lung compliance contributes at the same time to an increase in transpulmonary pressure (P_{tp}; *i.e.*, pressure inside alveoli minus pleural pressure) for a given insufflated V_T. In this regard, we reasoned that to study the effects of a decreased V_T on the accuracy of dynamic indexes in ARDS, we should also analyze effects on P_{tp} and esophageal pressure (P_{es}, pleural pressure) in this setting.[17,23] Moreover, to maintain minute volume ventilation in ARDS patients ventilated with low V_T, an increase in the respiratory rate (RR) is usually necessary.[20] This situation results in a lower number of heart beats being affected by each mechanical breath, a scenario that could also explain the low predictable value of ΔPP.[24] Indeed, Scharf *et al.*[25] have already demonstrated that RR affects "reverse pulsus paradoxus."

Because no study has evaluated the influence of V_T and RR on ΔPP in mechanically ventilated animals with ARDS-like symptoms, the present study sought to determine the influence of these parameters on ΔPP value during hemorrhagic shock in mechanically ventilated pigs with normal lungs or after lung lavage-induced acute lung injury (ARDS-like syndrome).

Materials and Methods

Approval from the Ethics Committee for Animal Research of the University Medical Center and by the Cantonal Veterinary Office of Geneva, Switzerland, was achieved before the study was initiated. Handling of animals followed the guidelines laid out in the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, 1996). We studied 24 domestic pigs (weight ± SD, 31.4 ± 3.1 kg). Five pigs were used for pilot experiments, optimizing the study protocol, and three animals were excluded because of technical problems. These eight animals were not analyzed. Animals were assigned to groups sequentially; *i.e.*, we started with the control animals and after eight animals, we proceeded with the animals subjected to ARDS.

General Procedure

Animals had free access to food and water until 12 h before the beginning of experiments. Premedication consisted of intramuscular injections of 6 mg/kg azaperon, 0.5 mg/kg midazolam, and 0.5 mg atropine. Anesthesia was induced by isoflurane inhalation and maintained by 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl, 1.5–2.0% isoflurane, and 0.4 $mg \cdot kg^{-1} \cdot h^{-1}$ pancuronium through a catheter placed into an ear vein. Depth of anesthesia was verified by paw pinch before muscular relaxation was administered. The animals were intubated and mechanically ventilated with oxygen in air (F_{IO_2} = 0.4 in control group [n = 8] and 1.0 in ARDS group [n = 8]) using a constant-volume respirator (Servo Ventilator 900; Siemens-Elema, Goeteborg, Sweden). No spontaneous breathing movements occurred during the experiments. V_T was initially set at 10 ml/kg and the RR at 15 breaths/min (RR15) with a positive end-expiratory pressure (PEEP) of 0 cm H_2O. Airway pressure and respiratory gases were continuously monitored (Ultima™; Datex/Instrumentarium, Helsinki, Finland). The right internal jugular vein, left internal carotid artery, and right femoral artery were cannulated for infusions, arterial pressure measurements, bleeding, and reperfusion. A flow-directed Swan-Ganz catheter (CCOmboV™, 7.5-French; Edwards Lifesciences, Irvine, CA) was introduced through the right internal jugular vein and advanced into the pulmonary artery to measure central venous pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, continuous cardiac output, and continuous mixed venous saturation. Arterial pressure tracings and mean arterial pressure were measured by a left carotid arterial catheter advanced into the descending aorta. Vascular pressures were measured using calibrated pressure transducers (Honeywell, Zürich, Switzerland) positioned at the level of the left atrium. A standard 3-lead electrocardiogram was continuously displayed on a Hewlett-Packard monitor (M3150A; Hewlett-Packard, Andover, MA) with digital readout of heart rate by means of cutaneous electrodes. Diuresis was monitored by a suprapubic catheter.

Respiratory Mechanics

Airway pressure was measured and V_T calculated by digital integration of a flow signal measured by a pneumotachograph (Godart 17212; Gould Electronics BV, Bilthoven, Netherlands), the two connected to the endotracheal tube. This setting permitted continuous breath by breath assessment of dynamic compliance of the respiratory system (C_{RS} = V_T/[plateau airway pressure − PEEP]) and expiratory airway resistance (R_{aw} = [plateau airway pressure − PEEP]/maximal expiratory air flow)[26] from three respiratory cycles. Measurement of P_{es} was used to estimate pleural pressure and calculate P_{tp} by means of an inflatable latex double-balloon catheter (Ref C48 Sde Guenard; Marquat Génie Biomédical, Boissy-Saint-Léger, France) advanced into the esophagus with the distal balloon placed into the stomach and the proximal balloon in the esophagus behind the heart.[27] The two balloons were filled with air to a volume of 0.5 to 1 ml. Continuous P_{tp} was calculated by subtracting

Table 1. Characteristics of Hemodynamic Variables of the Control and ARDS Groups (Combined Ventilated Groups)

	Baseline	
Hemodynamic Variables	Control	ARDS
MAP, mmHg	93.2 (86.8−99.6)	83.3 (77.1−89.6)*
MPAP, mmHg	22.9 (21.1−24.7)	28.2 (26.4−29.9)‡
CVP, mmHg	7.7 (7.0−8.5)	7.4 (6.7−8.2)
PCWP, mmHg	9.7 (8.8−10.6)	9.5 (8.7−10.3)
HR, beats/min	98 (87−110)	158 (147−169)‡
CO, l/min	5.9 (5.2−6.6)	7.0 (6.4−7.7)†
SVR, dynes · s · cm^{-5}	1,207 (1,074−1,340)	883 (762−1005)‡
PVR, dynes · s · cm^{-5}	188 (156−221)	216 (186−245)
ΔPP, %	6.1 (5.2−7.1)	5.2 (4.3−6.1)

Data are means with 95% confidence intervals in parentheses, n = 8 animals including all three ventilatory conditions.

*$P < 0.05$ *vs.* respective control. †$P < 0.001$ *vs.* respective baseline. ‡$P < 0.001$ *vs.* respective control. §$P < 0.01$ *vs.* respective baseline. ‖$P < 0.05$ *vs.* respective baseline. #$P < 0.01$ *vs.* respective control.

ARDS = acute respiratory distress syndrome; CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; ΔPP = change in pulse pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

simultaneous P_{es} from plateau airway pressure, and tidal P_{tp} (ΔP_{tp}) was determined as the amplitude of P_{tp} swings during each mechanical breath. Tidal P_{es} (ΔP_{es}) was also measured (*i.e.*, amplitude of P_{es} swings during a mechanical breath).

Hemodynamics

Systemic vascular resistance was calculated by dividing the difference between mean arterial pressure and central venous pressure measured at end-expiration by cardiac output, pulmonary vascular resistance by dividing the difference between mean pulmonary arterial pressure and pulmonary capillary wedge pressure by cardiac output. ΔPP was defined as the difference between the maximal and minimal values of pulse pressure divided by the average of the pulse pressure during a respiratory cycle.[8]

Blood gas tensions, oxygen hemoglobin saturation and pH were intermittently analyzed by an automated oximeter (ABL-505 analyser; Radiometer, Copenhagen, Denmark). Arteriovenous oxygen content difference, intrapulmonary shunt, oxygen transport, oxygen extraction ratio, and oxygen consumption were calculated using standard formulae from the blood gas analysis and cardiac output measurement.

The different continuously recorded hemodynamic and respiratory measurements were stored at a sampling rate of 200 Hz *via* an analog/digital interface converter (Biopac, Santa Barbara, CA) on a personal computer for off-line analysis. In all groups, lactated Ringer's solution was adminis-

Table 2. Characteristics of Respiratory Variables of the Control and ARDS Groups (Combined Ventilated Groups)

	Baseline	
Variable	Control	ARDS
Lung Mechanics		
C_{rs}, ml/cm H_2O	27.8 (26.0-29.6)	17.3 (15.7-19.0)*
R_{aw}, cm $H_2O^{-1} \cdot s^{-1} \cdot ml^{-1}$	3.47 (2.54-4.40)	7.51 (6.66-8.36)*
ΔP_{tp}, cm H_2O	8.67 (7.43-9.91)	11.84 (10.66-13.03)*
ΔP_{es}, cm H_2O	0.59 (−0.63-1.82)	3.79 (2.70-4.88)*
Gas Exchange		
Pa_{O_2}/F_{IO_2}, mmHg	387 (359-415)	84 (59-109)*
Pa_{CO_2}, mmHg	49.2 (43.3-55.1)	73.8 (68.6-79.1)*
pHa, units	7.40 (7.37-7.44)	7.24 (7.21-7.27)*
Sa_{O_2}, %	95.8 (93.1-98.6)	87.1 (84.7-89.6)*
Sv_{O_2}, %	78.3 (74.4-82.2)	70.2 (66.6-73.8)‖
Qs/Qt, %	17.7 (12.2-23.2)	38.3 (33.4-43.3)*

Data are means with 95% confidence intervals in parentheses, n = 8 animals including all three ventilatory conditions.

*$P < 0.001$ *vs.* respective control. †$P < 0.001$ *vs.* respective baseline. ‡$P < 0.01$ *vs.* respective baseline. §$P < 0.05$ *vs.* respective baseline. ‖$P < 0.01$ respective control. #$P < 0.05$ respective control.

ARDS = acute respiratory distress syndrome; C_{rs} = dynamic respiratory system compliance; ΔP_{es} = tidal esophageal pressure; ΔP_{tp} = tidal transpulmonary pressure; Pa_{CO_2} = arterial partial pressure of carbon dioxide; Pa_{O_2}/F_{IO_2}= normalized arterial oxygenation ratio; pH_a = arterial pH; Qs/Qt = intrapulmonary shunt fraction; R_{aw}= expiratory airway resistance; Sa_{O_2} = arterial oxygen hemoglobin saturation; Sv_{O_2} = mixed venous oxygen hemoglobin saturation.

Table 1. Continued

Hemorrhage		Reperfusion	
ARDS	Control	ARDS	Control
60.7 (54.2–67.3)†	62.4 (56.0–68.8)†	94.6 (88.5–100.8)	85.9 (79.9–91.9)*
16.1 (14.9–17.4)†	23.8 (22.6–25.0)‡§	25.7 (24.3–27.2)	35.1 (33.7–36.5)†‡
5.6 (4.7–6.5)†	5.2 (4.2–6.1)†	10.3 (8.4–12.2)	8.5 (6.6–10.4)§
5.1 (4.4–8.8)†	7.0 (6.4–7.7)†‡	10.0 (9.2–10.8)	10.5 (9.8–11.2)
150 (134–166)†	213 (198–228)†‡	114 (103–126)§	175 (164–185)‡‖
3.2 (2.7–3.7)†	3.8 (3.4–4.3)†	5.7 (4.7–6.7)	7.2 (6.3–8.7)
1,342 (1,157–1,526)	1,229 (1,060–1,398)†	1,174 (1,001–1,348)	936 (778–1,094)*
278 (232–323)§	362 (321–404)†#	217 (181–253)	294 (261–327)†#
12.8 (10.3–15.3)†	11.8 (9.3–14.3)†	6.8 (5.5–8.1)	4.9 (3.6–6.2)*

tered at 5 ml · kg^{-1} · h^{-1} to compensate for basal fluid loss. The animal's central body temperature was maintained at approximately 37.5°C with a warm air fan.

Experimental Protocol

The different measured hemodynamic and respiratory variables were recorded during ventilation with a V_T of 10 or 6 ml/kg and RR15 or RR25. Three variants of ventilation were successively used: V_T10 ml/kg at RR15, V_T6 ml/kg at RR25, and V_T6 ml/kg at RR15. Each ventilation mode was used during 5–7 min under control conditions during baseline, after blood removal (hemorrhagic shock of ~30 min), and after reperfusion of the shed blood to restore normovolemia. The ratios of inspiratory time to expiratory time were not changed during the protocol. In the ARDS animal group, lung lavage-induced ARDS (~ 1 h, see below) followed the baseline step and preceded hemorrhage and reperfusion.

Lung Lavage. After switching F_{IO_2} to 1.0, surfactant depletion was performed by repetitive lung lavage, instilling 1,000 ml NaCl, 0.9%, at 37°C into the trachea.[28] The procedure was repeated 3.1 ± 0.3 (SD) times at 12.6 ± 3.5-min intervals until criteria for ARDS-like syndrome were fulfilled (*i.e.*, Pa_{O_2}/F_{IO_2} less than 200 mmHg). F_{IO_2} was kept at 1.0 throughout the remainder of the experiment in this group of pigs.

Bleeding and Reperfusion. Forty percent of total blood volume was removed during 5–10 min *via* the right femoral artery. Total blood volume was calculated as 75 ml/kg of body weight. The blood was stored in blood bags containing citrate-phosphate-dextrose (Baxter AG, Volketswil, Switzer-

Table 2. Continued

Hemorrhage		Reperfusion	
Control	ARDS	Control	ARDS
30.4 (28.2–32.5)†	22.7 (20.8–24.7)†*	27.4 (25.6–29.3)	19.3 (17.6–21.0)*†
3.22 (2.56–3.88)†	6.06 (5.46–6.66)‡*	3.48 (2.80–4.16)	6.79 (6.17–7.41)*
7.93 (6.78–9.08)	9.00 (7.90–10.10)†	8.93 (7.60–10.26)	10.57 (9.29–11.84)§
0.80 (–0.26–1.86)	3.38 (2.44–4.32)*	1.01 (–0.09–2.12)	3.45 (2.47–4.43)‖
367 (320–414)	197 (155–239)*†	375 (331–420)	163 (123–202)*†
53.5 (47.8–59.1)‡	71.9 (66.8–76.9)*	56.6 (48.9–64.3)†	82.8 (75.9–89.6)‡*
7.33 (7.27–7.39)	7.23 (7.18–7.28)#	7.45 (7.33–7.57)	7.20 (7.09–7.30)‡‖
91.5 (85.1–98.0)	95.7 (89.9–101.4)†	91.6 (85.3–97.9)	94.8 (89.3–100.4)†
64.6 (57.6–71.7)†	63.4 (56.8–69.9)	76.2 (70.6–81.7)	79.9 (74.7–85.1)‡
11.8 (8.1–15.6)§	9.0 (5.6–12.4)†	16.7 (10.2–23.1)	22.0 (16.1–27.8)†

land) and maintained at body temperature during continuous agitation until reperfusion. The time between the start of bleeding until completed reperfusion was 49 ± 5 min. The time between the start of bleeding and the start of reperfusion was 40 ± 4 min. The time between the end of bleeding and the start of reperfusion was 30 ± 4 min. The volume reperfused was 2.8 ± 0.3 ml · kg^{-1} · min^{-1}.

Statistics

Group data are presented as mean values with 95% confidence interval (CI) in parenthesis, representing the continuous online recordings averaged over 30-s periods immediately preceding the intermittent recordings of pulmonary capillary wedge pressure and blood gas samples taken before the change to the next ventilation pattern. A general linear full factorial analysis of variance (ANOVA) model with repeated measures procedure was used to analyze the effects of the successive interventions (time as within-subjects factor using four levels, allowing determination of the effect of lung lavage, hemorrhage, and reperfusion on the various dependent variables), as well as the overall difference between the two groups of animals (treatment group as between-subject factor) using PASW Statistics 18 software package (SPSS, Inc., Chicago, IL). In each separated treatment group, the associated interaction between the within-subjects factor "time" and the between-subjects factor "ventilatory mode" was also analyzed to determine the effect of the ventilatory mode on the dependent variables. The two-sided Dunnett test for multiple comparisons with baseline values was used for *post hoc* analysis when the ANOVA resulted in a *P* value less than 0.05. Furthermore, a one-way ANOVA for repeated measures was used to detect statistical significance between the three ventilatory modes in a given condition, followed by the Bonferroni *post hoc* test when the ANOVA resulted in a *P* value less than 0.05.

Results

Sixteen deeply sedated mechanically ventilated pigs were studied, eight in each group (control and ARDS). One set of recordings was lost in the control group during hemorrhage (animal 7; V_T6 ml/kg RR15 subgroup) and two sets in the ARDS group during control conditions (animal 11; V_T6 ml/kg RR15 and V_T6 ml/kg RR25 subgroups).

Effect of Lavage (Combined Ventilated Groups)

Lung alveolar lavage reproduced the expected hemodynamic, biologic, and respiratory characteristics of ARDS, with a 75% decrease in the Pa_{O_2}/F_{IO_2} ratio ($P < 0.001$ between treatment groups throughout time after baseline time point, even if there was some recovery of this ratio with time; tables 1 and 2). ΔPP remained unchanged. ΔP_{tp} as well as ΔP_{es} increased significantly after lung lavage (table 2).

Effect of Hemorrhage and Retransfusion (Combined Ventilated Groups)

After removal of 40% of total blood volume, there were marked expected changes in hemodynamic and respiratory variables (tables 1 and 2). Hemodynamics were similarly affected by hemorrhage in both control and ARDS pigs (table 1). However, compared with the control group and regarding lung mechanics, ΔP_{tp} decreased significantly after hemorrhage in the ARDS group (two-way ANOVA, group effect during hemorrhage; $P < 0.001$, table 2), whereas ΔP_{es} remained unchanged (table 2). Retransfusion of the shed blood completely corrected hemodynamic variables in the control and ARDS groups, except for a persistent tachycardia (both groups) and a pulmonary vasoconstriction (ARDS group).

Effect of Changing Ventilatory Pattern on ΔPP during Hemorrhage

In the control group, lowering ventilation to a V_T of 6 ml/kg reduced ΔPP by ~40% regardless of circulatory state ($P < 0.001$ *vs.* V_T of 10 ml/kg). Furthermore, at each hemodynamic state, ΔPP values during both reduced V_T modes were significantly different from those through the 10 ml/kg ventilation ($P < 0.01$; table 3) regardless of respiratory rates. Despite reduced absolute ΔPP values observed during low V_T ventilation, their overall time course (time effect) was not significantly different from the 1 s recorded when ventilating with the larger V_T (time × ventilation interaction; $P > 0.05$), and their response to hemorrhage remained significantly different from respective baseline conditions at all RR values ($P < 0.05$; table 3; fig. 1, controls). In contrast, in pigs subjected to ARDS, lowering ventilation to a V_T of 6 ml/kg rendered the ΔPP index unreliable for detecting hypovolemia regardless of the RR values (table 3; fig. 1, ARDS). However, when ΔPP was indexed and adjusted to ΔP_{tp} (fig. 1) and/or plateau pressure (Supplemental Digital Content 1, which is the figure displaying results, http://links.lww.com/ALN/A607), it became a reliable predictor for hypovolemia and reperfusion in ARDS animals ventilated with low V_T. A representative online recording of three consecutive periods of 20 s each at V_T10 ml/kg RR15, V_T6 ml/kg RR25, and V_T6 ml/kg RR15 is shown in figure 2.

Effect of Changing Ventilatory Pattern on Pulmonary Mechanics during Hemorrhage

The principal changes in pulmonary mechanics were as follows. First, significant changes in ΔP_{tp} in the control group after hemorrhage were absent, whereas a significant decrease in ΔP_{tp} was observed in the ARDS group (table 3 and fig. 3). Moreover, in this group, the hemorrhage-induced decrease in ΔP_{tp} values was proportionally larger (−22% [V_T6 ml/kg RR25] and −30% [V_T6 ml/kg RR15] compared with the decrease in pigs ventilated with a V_T of 10 ml/kg (−12%; fig. 3, table 3). In the ARDS group ventilated with low V_T, P_{es} values decreased significantly during hemorrhage compared with baseline ($P <$

Table 3. Effect of Changing Ventilatory Pattern on ΔPP, P_{es}, ΔP_{tp}, and ΔP_{es} in Control and ARDS Animals before and after Hemorrhage

	Baseline			Hemorrhage		
Groups	10/15	6/15	6/25	10/15	6/15	6/25
Control						
ΔPP, %	8.5 (7.1−9.9)	5.3 (4.1−6.6)*	5.0 (3.8−6.2)*	18.5 (15.3−21.7)†	11.0 (8.1−13.9)*†	9.8 (7.0−12.5)†‡
P_{es}, cm H_2O	3.4 (1.9−4.8)	3.2 (2.0−4.4)	3.3 (2.2−4.4)	2.5 (1.2−3.9)	3.1 (2.0−4.2)	2.8 (1.7−3.8)
ΔP_{tp}, cm H_2O	11.2 (9.1−13.4)	7.3 (5.3−9.3)§	7.9 (6.0−9.7)	10.6 (8.3−12.8)	6.7 (4.6−8.8)	7.0 (5.1−9.0)
ΔP_{es}, cm H_2O	0.58 (−0.06−1.21)	0.57 (0.08−1.05)	0.61 (0.13−1.10)	0.48 (−0.69−1.65)	0.51 (−0.37−1.39)	1.19 (0.31−2.07)
ARDS						
ΔPP, %	7.1 (5.3−9.0)	4.6(2.8−6.5)	4.0 (2.0−6.0)	20.1 (15.3−24.9)†	8.0 (3.2−12.9)*	7.7 (2.9−12.4)*
P_{es}, cm H_2O	5.3 (3.6−6.9)	3.9 (2.0−5.8)	5.0 (3.2−6.7)	3.9 (1.7−6.0)	1.7 (−0.8−4.1)‖	3.0 (0.8−5.3)‖
ΔP_{tp}, cm H_2O	15.2 (13.1−17.4)	10.6 (8.4−12.7)§	10.1 (8.0−12.2)*	13.0 (11.2−14.8)‖	7.1 (5.3−8.9)‡#	7.7 (5.9−9.5)‡‖
ΔP_{es}, cm H_2O	4.55 (2.08−7.01)	3.32 (0.47−6.16)	2.61 (−0.02−5.25)	4.58 (2.55−6.60)	3.06 (0.72−5.40)	1.87 (−0.29−4.04)

Data are means with 95% confidence intervals in parentheses; n = 8 animals.

*$P < 0.01$ *vs.* corresponding V_T10/RR15 ventilatory pattern. †$P < 0.05$ *vs.* respective baseline. ‡$P < 001$ *vs.* corresponding V_T10/RR15 ventilatory pattern. §$P < 0.05$ *vs.* corresponding V_T10/RR15 ventilatory pattern. ‖$P < 0.01$ *vs.* respective baseline. #$P < 001$ *vs.* respective baseline.

6/15 = V_T6 ml/kg, RR15; 6/25 = V_T6 ml/kg, RR25; 10/15 = V_T10 ml/kg, RR15; ARDS = acute respiratory distress syndrome; ΔP_{es} = tidal esophageal pressure; ΔPP = change in pulse pressure; ΔP_{tp} = tidal transpulmonary pressure; P_{es} = esophageal pressure; RR15 = respiration rate of 15 breaths/min; RR25 = respiration rate of 25 breaths/min.

0.01). However, no significant changes were observed in ΔP_{es} after hemorrhage regardless of V_T or RR values (table 3).

Discussion

The first finding of the present study was that after removal of 40% of total blood volume, ΔPP was a good indicator of hypovolemia in pigs with normal lungs and ventilated with low V_T of 6 ml/kg RR15 and/or RR25, the level of this hypovolemia indicator being just reduced by approximately 40% compared with larger V_T of 10 ml/kg. These results are in agreement with the cardiac output-preload dependency state anticipated by dynamic markers in critically ill patients

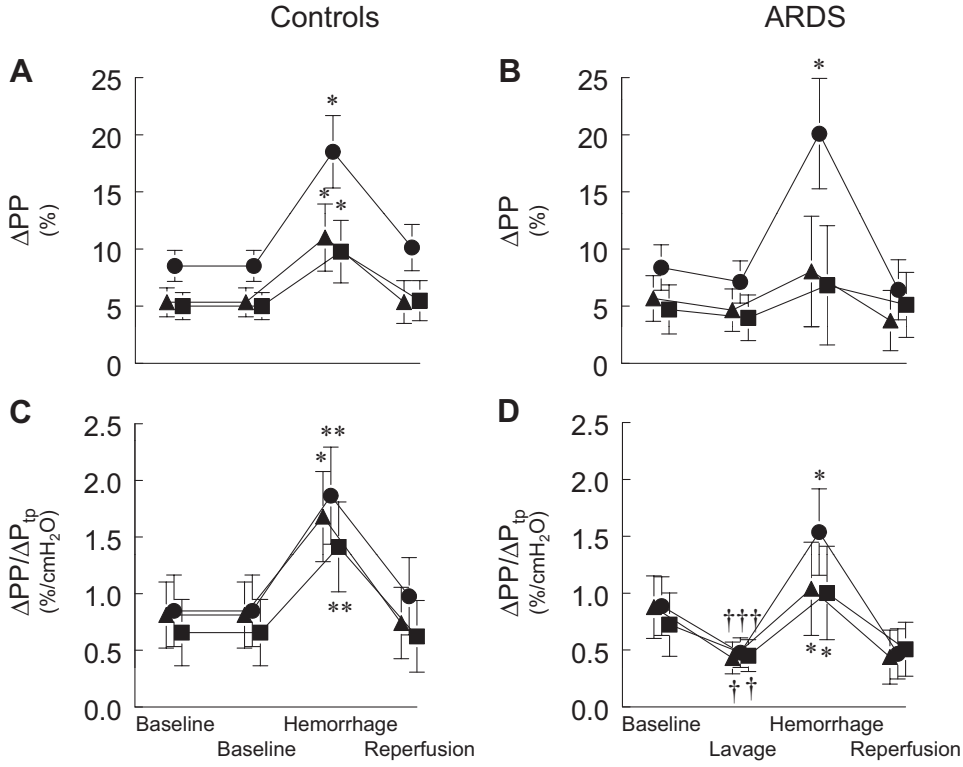

Fig. 1. Time course of change in pulse pressure (ΔPP) and ΔPP indexed to tidal transpulmonary pressure ($\Delta PP/\Delta P_{tp}$) in control animals (*A*, *C*) or animals with acute respiratory distress syndrome (ARDS) (*B*, *D*) alternatively ventilated for 5–7 min with a tidal volume (V_T) of 10 ml/kg and a respiratory rate of 15 breaths/min (RR15) (●), a V_T of 6 ml/kg and RR15 (▲), or a V_T of 6 ml/kg and RR25 (■). Data points are means with 95% confidence intervals; n = 8 animals. * $P < 0.05$; ** $P < 0.01$ *versus* baseline values (for control animals) and lavage values (for ARDS). † $P < 0.05$; ††† $P < 0.001$ *versus* baseline values.

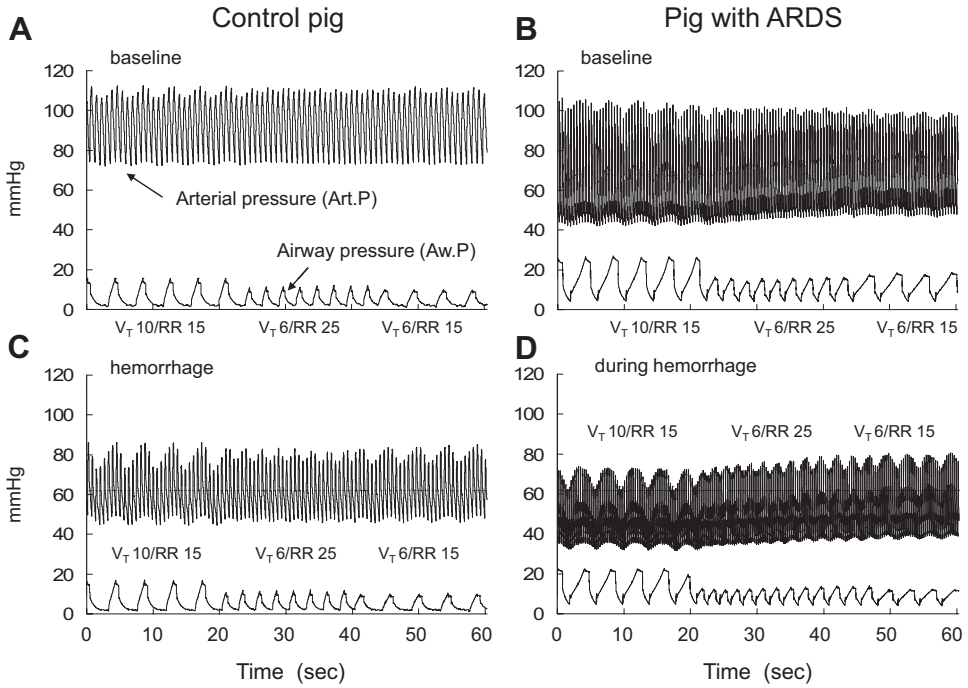

Fig. 2. Representative recording of systemic arterial pressure (Art.P) and airway pressure (Aw.P) in a control pig (*A*, *C*) and a pig with acute respiratory distress syndrome (ARDS) (*B*, *D*) successively ventilated for 20 s with the three investigated ventilatory patterns (*i.e.*, a tidal volume (V_T) of 10 ml/kg and a respiratory rate of 15 breaths/min [RR15], followed by a V_T of 6 ml/kg and RR25 and a V_T of 6 ml/kg and RR15 during baseline (*A*, *B*) and hemorrhage (*C*, *D*). Change in pulse pressure (ΔPP) was small before bleeding in pigs with normal lungs as well as those with ARDS, and it increased significantly during hemorrhagic shock in both groups, but mainly with a V_T of 10 ml/kg. Please observe that during baseline in pigs with ARDS, airway pressure gradient is more marked during V_T10 and V_T6 RR15 than during V_T6 RR25 but not during hemorrhage (impact of the decrease in ΔP_{tp} during bleeding).

with normal lungs and ventilated with low V_T.[29–31] However, our data highlight the result that ΔPP is not a sensitive marker of major changes in intravascular volume status in pigs affected by ARDS-like syndrome and ventilated with low V_T regardless of RR, except when this indicator was adjusted to ΔP_{tp} and/or plateau pressure.[18,19]

Because the slope of the Frank-Starling curve depends on ventricular contractility, static preload measurements are unable to anticipate the cardiac output-preload dependency.[3] In contrast, dynamic preload measurements, such as ΔPP determined by analysis of pulse pressure tracing, are useful in estimating the hemodynamic response to intravascular volume variations.[3,4,32] However, the magnitudes of dynamic preload indicators are also affected by V_T during acute lung injury.[16,33] Indeed, mechanical ventilation induces cyclic changes in intrathoracic and transpulmonary pressures, transiently affecting ventricular preload and leading to cyclic changes in stroke volume in preload-dependent but not in preload-independent patients. This phenomenon is related to the impact of inspiratory increase in intrathoracic pressure on pulmonary blood redistribution with changes in right ventricular outputs affecting left ventricular stroke volumes after two to three heart beats (pulmonary transit time).[34] According to this mechanism, inspiratory increase in left ventricular stroke volume results from delayed transmission through the pulmonary vasculature of the expiratory increase in right ventricular output and is followed by an expiratory decrease in left ventricular stroke volume as soon as the inspiratory decrease in right ventricular output has reached the left ventricle. If the decrease in right ventricular stroke volume after a mechanical breath is mainly related to decrease in venous return related to ΔP_{es} value in healthy lungs,[35] increase in ΔP_{tp} and right ventricular afterload could be an important determinant in lungs affected by ARDS.[23]

In this regard, in the present study, we have analyzed the impact of ΔP_{tp} and ΔP_{es} in this setting.[17,23] An important finding of the present study is that ΔP_{tp} increased after ARDS induction without significant changes in ΔP_{es} (tables 2 and 3). This fact highlights the idea that a decrease in C_{RS} in the ARDS group generates higher ΔP_{tp}. The major explanation for the inability of ΔPP to indicate hypovolemia in ARDS pigs ventilated with low V_T could be related to the increase in C_{RS} after hemorrhage compared with control animals (table 2). This fact produced a decrease in a ΔPP determinant (ΔP_{tp}) in the ARDS group during hemorrhage when ΔP_{tp} values in the control group did not change (fig. 3 and table 3). In addition, during hemorrhage, ΔP_{tp} in ARDS pigs ventilated with low V_T values decreased more significantly, compared with the matched baseline values, than in ARDS pigs ventilated with V_T of 10 ml/kg (fig. 3, table 3). The present explanation agrees with our results in that indexing ΔPP to ΔP_{tp} and/or plateau pressure made this marker a reliable predictor for hypovolemia

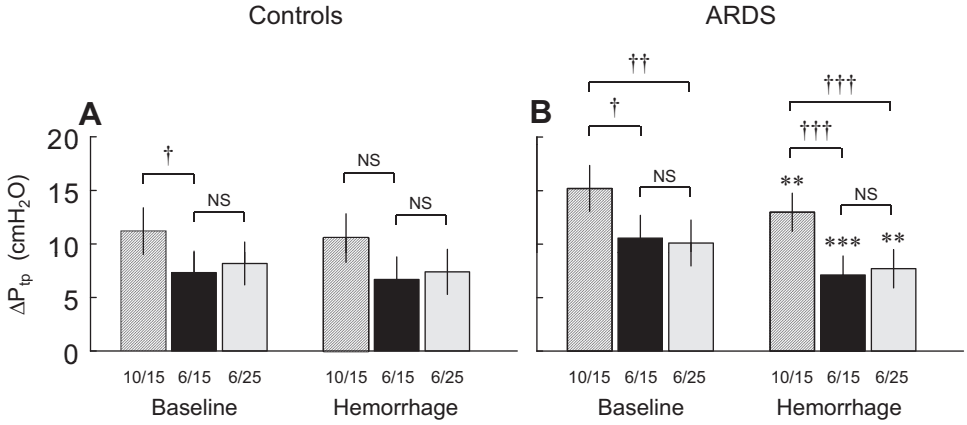

Fig. 3. Effect of hemorrhage on tidal transpulmonary pressure (ΔP_{tp}) in control pigs (*A*) and acute respiratory distress syndrome (ARDS) animals (*B*) before and after hemorrhage and alternatively ventilated with a tidal volume (V_T) of 10 ml/kg and a respiratory rate of 15 breaths/min (RR15), a V_T of 6 ml/kg and RR15, or a V_T of 6 ml/kg and RR25. *Bars* are means with 95% confidence intervals (*solid lines*); n = 8 animals; ** $P < 0.01$; *** $P < 001$ *versus* corresponding baseline values in control and ARDS animals, respectively; † $P < 0.05$; †† $P < 0.01$; ††† $P < 001$ *versus* corresponding V_T10 RR15 values. Note that compared with baseline, ΔP_{tp} during hemorrhage decreased significantly in the ARDS group regardless of the ventilatory pattern, whereas this was not the case in the control group.

and reperfusion (fig. 1 and Supplemental Digital Content 1, http://links.lww.com/ALN/A607).[18,19] Because esophageal pressures are not usually available in patients, the present data highlight the value of ΔPP indexed to plateau pressure in this setting.[19]

We could also expect that ventilation without PEEP in ARDS pigs could have led to a decrease in functional residual capacity with an increase in chest wall compliance, inducing a decrease in the pressure transmitted to the pleural space during mechanical breath. In the ARDS group, during hemorrhage, P_{es} values decreased more significantly during low VT ventilation compared with baseline ($P < 0.01$, table 3). This feature could have affected ventricular preload, cyclic changes in stroke volume, and ΔPP in pigs affected by ARDS and ventilated with low VT. However, our data (table 3) do not support this assumption because no significant changes were observed in ΔP_{es} values in pigs with healthy lungs and/or those affected by ARDS-like syndrome. Indeed, changes in venous return, stroke volume, and ΔPP are related to ΔP_{es} and not P_{es}.

In the present study, we have also reasoned that the cause of impaired relevance of this dynamic index in this situation could be related to the high RR associated with low V_T in the ventilator setting of patients with ARDS and the impact of this fact on heart lung interactions.[16,24] With regard to this, we changed RR value during low V_T as maintaining optimal volume minute ventilation in ARDS lungs requires increase in RR.[20] The rationale was that the heart rate/RR ratio and V_T value are equally important as determinants of ΔPP.[24] Indeed, the number of heart beats affected by each mechanical breath is related to RR and inspiratory to expiratory time ratio. De Backer *et al.*[24] found that high RR (30–40 breaths/min) could limit the predictive value of ΔPP for fluid responsiveness. We did not find any impact of RR on the reliability of ΔPP to detect hypovolemia in animals ventilated with low V_T probably for two reasons. First, compared with De Backer *et al.*,[24] our highest level of RR was only 25 breaths/min in ARDS animals, which, in combination with tachycardia (table 1), made heart rate/RR unchanged in ARDS animals. Second, as stated previously, our model generated a change in respiratory mechanics that affected ΔP_{tp} as a determinant of ΔPP during hypovolemia.

The present animal study acknowledges some limitations. First, as discussed before, we used a low level of PEEP in the present animal study, whereas patients with ARDS ventilated with smaller V_T are often treated with high levels of PEEP, which could have an impact on transpulmonary pressures and the pressures transmitted to pleural spaces. Second, our model of ARDS produces major changes in heart rate and respiratory mechanics, and we cannot exclude the idea that ΔPP would be insensitive to changes in volemia in the absence of major changes in these variables. Third, the internal carotid artery is closer to the central (aortic) pressure than the radial artery, and this fact could have affected ΔPP results. However, because the animals used in our experiments were healthy pigs, we expect that a peripheral artery would have been a less acceptable approach to measure pulse pressure, because the compliant aorta would have markedly buffered stroke volume.[36] Finally, the minor rise in diastolic pressure in pigs ventilated with low V_T during ARDS (fig. 3) suggests that a steady state was difficult to achieve and could have affected measurements.

In conclusion, we found ΔPP to be a reliable indicator of severe hypovolemia in pigs with healthy lungs regardless of V_T or RR. In pigs affected by severe ARDS-like syndrome and ventilated with low PEEP, the measured index remains a valid indicator of severe hypovolemia at V_T of 10 ml/kg but a less sensitive indicator at V_T of 6 ml/kg. However, ΔPP indexed to ΔP_{tp} and/or plateau pressures were reliable gauges of blood volume status.

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References

1. Arieff AI: Fatal postoperative pulmonary edema: Pathogenesis and literature review. Chest 1999; 115:1371–7
2. Boussat S, Jacques T, Levy B, Laurent E, Gache A, Capellier G, Neidhardt A: Intravascular volume monitoring and extravascular lung water in septic patients with pulmonary edema. Intensive Care Med 2002; 28:712–8
3. Bendjelid K, Romand JA: Fluid responsiveness in mechanically ventilated patients: A review of indices used in intensive care. Intensive Care Med 2003; 29:352–60
4. Michard F, Teboul JL: Predicting fluid responsiveness in ICU patients: A critical analysis of the evidence. Chest 2002; 121:2000–8
5. Feissel M, Badie J, Merlani PG, Faller JP, Bendjelid K: Pre-ejection period variations predict the fluid responsiveness of septic ventilated patients. Crit Care Med 2005; 33:2534–9
6. Feissel M, Teboul JL, Merlani P, Badie J, Faller JP, Bendjelid K: Plethysmographic dynamic indices predict fluid responsiveness in septic ventilated patients. Intensive Care Med 2007; 33:993–9
7. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL: Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 2000; 162:134–8
8. Michard F, Chemla D, Richard C, Wysocki M, Pinsky MR, Lecarpentier Y, Teboul JL: Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. Am J Respir Crit Care Med 1999; 159:935–9
9. Tavernier B, Makhotine O, Lebuffe G, Dupont J, Scherpereel P: Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. ANESTHESIOLOGY 1998; 89:1313–21
10. Barbier C, Loubières Y, Schmit C, Hayon J, Ricôme JL, Jardin F, Vieillard-Baron A: Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. Intensive Care Med 2004; 30:1740–6
11. Bendjelid K, Suter PM, Romand JA: The respiratory change in preejection period: A new method to predict fluid responsiveness. J Appl Physiol 2004; 96:337–42
12. Feissel M, Michard F, Faller JP, Teboul JL: The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med 2004; 30:1834–7
13. Feissel M, Michard F, Mangin I, Ruyer O, Faller JP, Teboul JL: Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. Chest 2001; 119:867–73
14. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL: Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients. Intensive Care Med 2005; 31:1195–201
15. Vieillard-Baron A, Chergui K, Rabiller A, Peyrouset O, Page B, Beauchet A, Jardin F: Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. Intensive Care Med 2004; 30:1734–9
16. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL: Pulse pressure variations to predict fluid responsiveness: Influence of tidal volume. Intensive Care Med 2005; 31:517–23
17. Teboul JL, Vieillard-Baron A: Clinical value of pulse pressure variations in ARDS. Still an unresolved issue? Intensive Care Med 2005; 31:499–500
18. Lefrant JY, De Backer D: Can we use pulse pressure variations to predict fluid responsiveness in patients with ARDS? Intensive Care Med 2009; 35:966–8
19. Vallée F, Richard JC, Mari A, Gallas T, Arsac E, Verlaan PS, Chousterman B, Samii K, Genestal M, Fourcade O: Pulse pressure variations adjusted by alveolar driving pressure to assess fluid responsiveness. Intensive Care Med 2009; 35:1004–10
20. 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. N Engl J Med 2000; 342:1301–8
21. Brower RG, Rubenfeld GD: Lung-protective ventilation strategies in acute lung injury. Crit Care Med 2003; 31:S312–6
22. Jardin F, Genevray B, Brun-Ney D, Bourdarias JP: Influence of lung and chest wall compliances on transmission of airway pressure to the pleural space in critically ill patients. Chest 1985; 88:653–8
23. Scharf SM, Caldini P, Ingram RH Jr: Cardiovascular effects of increasing airway pressure in the dog. Am J Physiol 1977; 232:H35–43
24. De Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL: Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. ANESTHESIOLOGY 2009; 110:1092–7
25. Scharf SM, Brown R, Saunders N, Green LH: Hemodynamic effects of positive-pressure inflation. J Appl Physiol 1980; 49:124–31
26. Chapter 30: Rossi A, Polese G, Milic-Emili J: Monitoring respiratory mechanics in ventilator-dependent patients, Principles and Practice of intensive care monitoring, 3rd edition. Edited by Tobin MJ. New York, McGraw Hill, 1998, pp 553–96
27. Milic-Emili J, Mead J, Turner JM, Glauser EM: Improved technique for estimating pleural pressure from esophageal balloons. J Appl Physiol 1964; 19:207–11
28. Lachmann B, Robertson B, Vogel J: In vivo lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesiol Scand 1980; 24:231–6
29. Marx G, Cope T, McCrossan L, Swaraj S, Cowan C, Mostafa SM, Wenstone R, Leuwer M: Assessing fluid responsiveness by stroke volume variation in mechanically ventilated patients with severe sepsis. Eur J Anaesthesiol 2004; 21:132–8
30. Rex S, Brose S, Metzelder S, Hüneke R, Schälte G, Autschbach R, Rossaint R, Buhre W: Prediction of fluid responsiveness in patients during cardiac surgery. Br J Anaesth 2004; 93:782–8
31. Wiesenack C, Fiegl C, Keyser A, Prasser C, Keyl C: Assessment of fluid responsiveness in mechanically ventilated cardiac surgical patients. Eur J Anaesthesiol 2005; 22:658–65
32. Michard F, Reuter DA: Assessing cardiac preload or fluid responsiveness? It depends on the question we want to answer. Intensive Care Med 2003; 29:1396–7
33. Romand JA, Shi W, Pinsky MR: Cardiopulmonary effects of positive pressure ventilation during acute lung injury. Chest 1995; 108:1041–8
34. Hoffman JI, Guz A, Charlier AA, Wilcken DE: Stroke volume in conscious dogs; effect of respiration, posture, and vascular occlusion. J Appl Physiol 1965; 20:865–77
35. Theres H, Binkau J, Laule M, Heinze R, Hundertmark J, Blobner M, Erhardt W, Baumann G, Stangl K: Phase-related changes in right ventricular cardiac output under volume-controlled mechanical ventilation with positive end-expiratory pressure. Crit Care Med 1999; 27:953–8
36. Lamia B, Teboul JL, Monnet X, Osman D, Maizel J, Richard C, Chemla D: Contribution of arterial stiffness and stroke volume to peripheral pulse pressure in ICU patients: An arterial tonometry study. Intensive Care Med 2007; 33:1931–7